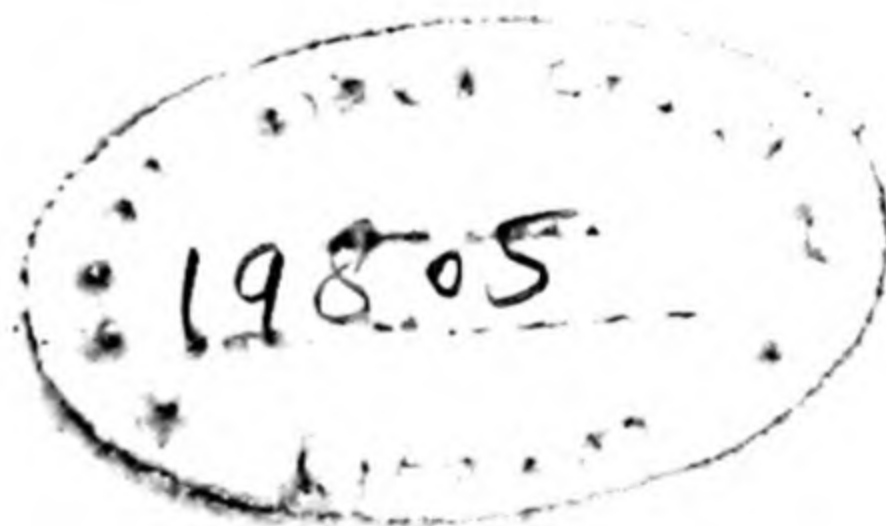


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ORGANIC CHEMISTRY



Reinhold Chemistry Textbook Series

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University of Florida
Gainesville, Florida

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Holland, Michigan

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Consulting Editors' Statement

During the past three decades, organic chemistry has emerged as a vigorous and relatively exact science based on well-developed theory. The belief that beginning students of organic chemistry should be taught not only the facts of the subject, but also the framework of principles which tie these facts together into a unified science, is now shared by almost all teachers in the field. But how to teach the two in proper balance—how to present mechanisms of organic reactions in a context which will have relevance and meaning for the beginning student—this is a question which faces every serious teacher of organic chemistry.

This is precisely the question which the authors of *Organic Chemistry* have asked; their answer, which has grown out of their broad background of teaching experience, is embodied in the text. Many other thoughtful teachers have arrived at the same answer. Now, for the first time, this fundamentally new approach to the teaching of organic chemistry is available in text form.

Reviewing, first, important basic principles of chemistry with emphasis on their application to organic chemistry, Professors Smith and Cristol proceed to a factual treatment of organic chemistry using the structural theory as the basis for describing the behavior of the simple functions. This sets the stage for a thorough explanation and correlation of reactions through a completely modern presentation of the theory of reaction mechanisms. Factual and descriptive chemistry, and theory and reaction mechanisms, are presented in ideal balance.

By this arrangement, the authors exploit dual advantages. First of all, they present the "how" of reactions at the precise time the student really wants to know. They avoid the common mistake of solving problems the student doesn't have. Second, the authors capitalize on the pedagogical advantage of review, in a sound manner, with maximum efficiency. Every experienced teacher of organic chemistry realizes the value of review; in *Organic Chemistry* Professors Smith and Cristol have shown how it can be accomplished without loss of time and effort.

In the last section of the text, the chemistry of the simple functions and the theory of reaction mechanisms are blended in a study of special topics dealing with more complex substances. Here the student is provided with excellent opportunity to test his knowledge and understanding by actual application to significant practical cases.

The presentation is enlivened and sharpened throughout by the inclusion of a wealth of stimulating and provocative questions and problems and of a host of exceptionally significant drawings and illustrations designed to assist the student in grasping concepts and understanding principles.

CALVIN A. VANDERWERF
HARRY H. SISLER



Model of the DNA Molecule. Courtesy Dr. A. Hodge of California Institute of Technology and Dr. A. Kornberg of Stanford University. Dr. Kornberg shared the Nobel Prize in medicine in 1959 for his enzymatic synthesis of DNA.

AL-SY

Organic Chemistry

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(AN EAST - WEST EDITION)

AFFILIATED EAST-WEST PRESS PVT. LTD.
NEW DELHI

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East-West Student Edition -

Price : Rs. 21.75



Sales Territory : India, Burma, Ceylon, Malaysia and Singapore.

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This book has been published with the assistance of the Joint Indian-American Textbook Programme.

Published by K. S. Padmanabhan for AFFILIATED EAST-WEST PRESS PVT. LTD., 9 Nizamuddin East, New Delhi 13, India; and printed by G. D. Makhija at the India Offset Press, Delhi.

To
Creig Simmons Hoyt
Charles DeWitt Hurd
and
William Gould Young,
inspiring men and stimulating teachers,
this book is respectfully dedicated.

Preface

The principal aim of this, and presumably any other organic chemistry textbook, is to enable the student beginning a study of the subject to gain an effective comprehension of this immense field with relative ease. To accomplish this end, such a text must present a sound body of experimental facts in a systematic organization, correlated and explained by the best and the most recent basic theories possible. The presentation must start at the average level of its intended audience, and gradually lift each student to the highest practicable level of achievement.

In the past, organic chemistry was organized entirely by functional groups, with everything factual and theoretical in one impenetrable lump under the functional heading. Recent texts have introduced a commendable trend in teaching based on reaction types and mechanisms rather than functional groups. However, in espousing mechanism, some of these have gone to the opposite extreme and omitted much that is good in classical organic chemistry. In minimizing factual, descriptive material, they have been forced to a presentation that begins for many students nowhere near the introductory level.

The authors of this text feel that they have combined the best features of both presentations in an original organization that accomplishes well, in their experience, the aims elaborated in the first paragraph above. This text begins in the first unit with an introduction to the nature and scope of organic chemistry and reviews briefly important principles many students miss or ignore in their general chemistry courses, this review being slanted toward the utilization of these principles in organic chemistry.

The second unit provides the factual foundation for later mechanistic development. It establishes structural theory as the basis of the behavior of the simple functions. Nomenclature, uses, and important methods of preparation are considered. Effort is expended to give the student the feeling that organic chemistry is a tangible, practical endeavor, not just an ethereal philosophy.

In the third unit theory and mechanism are exploited to correlate reactions. Syntheses are emphasized for the first time. Problems develop the student's skill in devising synthetic schemes from single step to multiple step outlines involving ten or more reactions.

The fourth and fifth units provide more descriptive material, also inter-

laced with theory, in topics that are of vital concern, not to all organic chemists, but some to each one. The teacher using the text can select from among these the topics that best suit his preference or the needs of his students. All those constitutive properties that figure substantially in the field of organic chemistry are included, not merely optical activity. Important recent developments in the fields of complex substances and metabolic materials, such as enzymes and nucleic acids, are included with the usual carbohydrates and proteins. While some of these topics may reach a fair distance into the field of biochemistry, the authors consider this necessary since not all students will take a course in biochemistry. For those who can, this material provides a sound basis for biochemistry. It is hoped that each student will gain the feeling that organic chemistry is of vital importance to himself, not just as a subject to study, but as a body of knowledge that influences his daily living. A further hope is that many will find this an introduction to an exciting intellectual discipline to which they can devote lifetimes of rewarding study and practice.

The authors have received helpful suggestions from a large number of persons, including colleagues and former students. They wish particularly to acknowledge rather extensive aid in manuscript reading and criticism by Dr. Ronald Caple, Dr. Robert H. DeWolfe, Mr. Bruce B. Jarvis, Dr. Gwen Mayo, Dr. John S. Meek, and Mr. Terence C. Morrill.

January, 1966

L. OLIVER SMITH, JR.
STANLEY J. CRISTOL

Contents

UNIT I INTRODUCTION	1
1. The Nature and Study of Organic Chemistry	3
1-1 The Term Organic Chemistry 1-2 Suggestions for Study	
2. Molecular Weights	6
2-1 Determination of Molecular Weights 2-2 Molecular Weight from Vapor Density 2-3 Molecular Weight from Freezing and Boiling Points 2-4 Molecular Weights from Other Physical Properties	
3. Formulation	11
3-1 Determination of Composition of Carbon Compounds 3-2 Formulas, Structures, and Configurations	
4. Bonding and Chemical Reactivity	20
4-1 Principles which Underlie Chemical Bonding 4-2 Molecular Properties 4-3 Carbon and Its Properties 4-4 Use of Inorganic Reagents in Organic Chemistry	
UNIT II FUNDAMENTAL PRINCIPLES OF ORGANIC STRUCTURE AND CLASSIFICATION	57
5. Constitution of Organic Compounds	59
5-1 Carbon Skeletons 5-2 Functional Groups and Classification of Compounds	
6. Nomenclature	91
6-1 Trivial Names 6-2 Early Systems 6-3 The IUPAC System 6-4 Chemical Abstracts Nomenclature 6-5 Nomenclature Tables	
7. Fundamental Chemical Properties	117
7-1 Single Bonds 7-2 Multiple Bonds 7-3 Group Interactions	
8. Classical Methods for the Determination of Structure	163
8-1 Principles of Structural Proof 8-2 Typical Classical Problems and Their Solutions	
9. Structure and Physical Properties	179
9-1 Simply Determined Properties 9-2 Brief Survey of Constitutive Properties	
UNIT III ORGANIC REACTIONS	203
10. Acidity and Basicity in Organic Compounds	205
10-1 Definitions of Acids and Bases 10-2 Acidity and Organic Acids 10-3 Basicity and Basic Organic Compounds	

11. Factors Influencing Chemical Reactions and Reactivities	226
11-1 Basic Principles 11-2 Fundamental Reaction Types	
11-3 Chemical Equilibria and Reaction Rates 11-4 Types of	
Reactive Intermediates 11-5 Types of Ionic Reagents;	
Electrophiles and Nucleophiles 11-6 Steric Factors; Molecu-	
lar Geometry 11-7 Resonance in Conjugated Systems	
11-8 Catalysis 11-9 Principles of Synthesis	
12. Nucleophilic Displacements on Saturated Carbon Atoms	260
12-1 Replacements of Halides, Sulfates, and Sulfonates	
12-2 Nucleophilic Replacements in Alcohols and Ethers	
13. Elimination Reactions	292
13-1 Beta Eliminations 13-2 Pyrolytic <i>cis</i> -Eliminations	
13-3 1,4-Conjugate Eliminations 13-4 Eliminations Involv-	
ing Internal Replacements 13-5 Alpha Elimination Reac-	
tions. Carbenes and Methylenes	
14. Electrophilic Additions to Carbon-Carbon Multiple Bonds	314
14-1 General Reactivities of Multiple Bonds 14-2 Electro-	
philic Additions 14-3 Additions to Acetylenes. Vinylation	
15. Halogenation and Addition by Free Radical Processes	329
15-1 The Homolytic, or Free Radical, Process 15-2 Chlorina-	
tion of Methane, A Typical Free Radical Chain Reaction	
15-3 Positional Selectivity of Radical Reactions 15-4 Addi-	
tion to Carbon-Carbon Double Bonds 15-5 Energy Require-	
ments of Free Radical Chains 15-6 Conjugate Free Radical	
Addition	
16. Electrophilic Aromatic Substitution	338
16-1 Nature of Electrophilic Aromatic Substitution 16-2 Cor-	
relation of Structure with Reactivity in Aromatic Compounds	
16-3 Electrophilic Reagents 16-4 Substituent Effects	
16-5 Representative Reactions 16-6 Side Reactions	
17. Nucleophilic Additions and Displacements at Unsaturated Atoms	
I. Additions and Displacements in Acid Derivatives: Solvolysis	371
17-1 Nucleophilic Displacement Reactions. Addition-	
Elimination Mechanism 17-2 Ester Interchange as a Typical	
Nucleophilic Displacement 17-3 Solvolysis of Acid Deriva-	
tives and Acids 17-4 Side Reactions 17-5 Solvolysis in	
Sulfonic Acid Derivatives	
18. Nucleophilic Additions and Displacements at Unsaturated Atoms	
II. Reactions of Aldehydes, Ketones, and Nitriles	392
18-1 General Mechanisms for Nucleophilic Addition	
18-2 Addition Products of Aldehydes, Ketones, and Nitriles	
18-3 Addition to Cumulated Unsaturated Systems 18-4 Car-	
bonyl Oxygen Displacements	

19. Organometallic Compounds and Organometalloids	420
19-1 Nomenclature 19-2 Preparation 19-3 Typical Organometallic Compounds 19-4 Special Handling Problems 19-5 Chemical Reactions	
20. Nucleophilic Displacements and Additions in Unsaturated Systems	
III. Grignard Syntheses and Hydride Reductions	436
20-1 Grignard Syntheses and Similar Reactions by Other Organometallic Compounds 20-2 Reduction by Metal Hydrides	
21. Reactions of "Active Hydrogen" Compounds. Enols and Enolates as Intermediates	448
21-1 General Considerations 21-2 Keto-Enol and Analogous Transformations 21-3 The Haloform Reaction 21-4 Condensations 21-5 Aromatic Ring Condensations 21-6 Malonic and Acetoacetic Ester Syntheses 21-7 Decarboxylation Reactions	
22. Nucleophilic Reactions at Unsaturated Carbon	
IV. Reactions at Carbon-Carbon Multiple Bonds: Conjugate Addition, Vinylation, and Nucleophilic Aromatic Substitution	473
22-1 Introduction 22-2 Additions to Acrylonitrile. Cyanoethylation 22-3 Additions to α,β -Unsaturated Aldehydes, Ketones, and Esters 22-4 Michael Addition Reactions 22-5 Additions to Acetylenes. Vinylation 22-6 Aromatic Nucleophilic Displacements 22-7 Nucleophilic Displacements in Vinyl Halides 22-8 Aromatic Nucleophilic Displacements Via Aryne Intermediates. Elimination-Addition Mechanisms	
23. Oxidation-Reduction Systems which Involve Hydride Exchange	488
23-1 The Cannizzaro Reaction 23-2 The Tishchenko Reaction 23-3 The Meerwein-Ponndorf-Verley and Oppenauer Reactions 23-4 The Benzoin Condensation	
24. Diazonium Compounds and Diazo Compounds	495
24-1 Preparation 24-2 Properties and Reactions of Diazonium Salts 24-3 Properties and Reactions of Diazo Compounds 24-4 Other Related Eliminations of Nitrogen. The Wolff-Kischner Reduction	
25. Molecular Rearrangements	510
25-1 Violations of the Rule of Minimum Structural Change 25-2 Rearrangements Involving Electron-Deficient Intermediates. General Concepts 25-3 Migrations to Electron-Rich Carbon Atoms 25-4 Aromatic Rearrangements 25-5 The Willgerodt Reaction	

26. Free Radical Reactions	532
26-1 Nature of Free Radicals 26-2 Evidence for Free Radicals	
26-3 Formation of Free Radicals and Initiation of Free Radical Processes 26-4 Free Radical Reactions 26-5 Stereochemistry in Free Radical Reactions 26-6 Fragmentation of Free Radicals 26-7 Free Radical Rearrangements 26-8 Radical Ions 26-9 Diradicals	
27. Oxidation	550
27-1 Oxidation by Air and Oxygen 27-2 Oxidation by Reagents in Solution 27-3 Organic Peroxy Compounds	
28. Reduction	572
28-1 Hydrogenation and Hydrogenolysis 28-2 Reduction by Metals 28-3 Miscellaneous Reducing Agents	
29. Cycloadditions	588
29-1 Diene Synthesis 29-2 Bridged Polycyclic Compounds 29-3 Cyclobutane Ring Formation	
UNIT IV CONSTITUTIVE PHYSICAL PROPERTIES	601
30. Index of Refraction	603
30-1 Theory of Refraction of Light 30-2 Measuring Refractive Index 30-3 Use of Refractive Index	
31. Optical Activity	609
31-1 Polarized Light 31-2 Optically Active Substances 31-3 Molecular Basis of Optical Activity 31-4 Conventions for Configurational Formulas 31-5 Asymmetric Carbon Atoms 31-6 Racemic Modifications 31-7 Asymmetric Molecules without Asymmetric Atoms 31-8 Physical Properties of Optical Isomers 31-9 Preparation of Optically Active Compounds	
32. Optical Rotatory Dispersion	633
32-1 Dispersion 32-2 Absorption of Light 32-3 The Cotton Effect 32-4 Measurement of Optical Rotatory Dispersion 32-5 Structure and Optical Rotatory Dispersion	
33. Color and Spectra	639
33-1 Spectra and Absorption of Light 33-2 Molecular Spectra 33-3 Dyes and Dyeing 33-4 Indicators	
34. Magnetic Resonance	667
34-1 Spin Properties of Atomic Particles 34-2 Apparatus for Detecting and Measuring Magnetic Resonance 34-3 NMR Spectra 34-4 Electron Paramagnetic Resonance Spectra	
35. Electric Dipole Moments	676
35-1 Behavior of Polar Molecules 35-2 Relationship of Dipole Moment to Structure	

36. Diffraction	684
36-1 Theory of Diffraction 36-2 Diffraction Techniques	
37. Mass Spectra	689
37-1 Positive Ion Beams 37-2 Molecular Mass Spectra	
37-3 Molecular Ionizing Energies	
UNIT V TOPICS OF SPECIAL INTEREST	693
38. Carbohydrates	695
38-1 Carbohydrates 38-2 Metabolism of Carbohydrates	
38-3 Constituents of Wood	
39. Amino Acids and Proteins	731
39-1 Amino Acids 39-2 Proteins 39-3 Enzymes	
40. Fats, Oils, Waxes, and Detergents	754
40-1 Lipids 40-2 Waxes 40-3 Soaps and Other Detergents	
40-4 Compound Lipids	
41. Terpenes and Steroids	770
41-1 Terpenes 41-2 Steroids	
42. Heterocycles	785
42-1 Simple and Common Fused Heterocycles and Their Derivatives 42-2 Porphyrins 42-3 Pyrimidines, Purines, and Nucleic Acids	
43. Physiological Action and Molecular Constitution	815
43-1 Vitamins 43-2 Hormones 43-3 Pesticides 43-4 Chemo- therapy	
44. Petroleum Products	834
44-1 Petroleum Refining 44-2 Petroleum Products	
45. Silicon Organic Compounds and Fluorocarbons	841
45-1 Special Nature of Silicon Organics 45-2 Simple Organo- silicon Compounds 45-3 Silicones 45-4 Uses of Silicon Organic Materials 45-5 Fluorocarbons	
46. Polymerization and Polymers	850
46-1 Polymerization 46-2 Natural and Synthetic Rubbers	
46-3 Plastics 46-4 Physical Modification of Polymers	
46-5 Condensation Polymers	
Appendix I List of Reference Works for Organic Chemistry	871
Appendix II Glossary and Index of Named Reactions	876
Appendix III General Nomenclature Tables	892
Appendix IV Answers to Selected Questions and Problems	912
Index	937

UNIT



Introduction



The Nature and Study of Organic Chemistry

1-1 THE TERM ORGANIC CHEMISTRY

Originally, organic compounds were those carbon compounds obtained from living organisms. One of the interesting developments of the nineteenth century was the overthrow of the idea that such compounds as sugar, urea, and alcohol could be prepared only by the help of a "vital force" supposed to exist in all living organisms. While many substances, such as starches, proteins, and a few natural drugs, are so complex that they have defied the ingenuity of organic chemists, most compounds found in plants and animals can be and have been prepared in the laboratory with the help of no living creature other than the chemist. Chemists have gone far beyond nature to produce drugs, pesticides, textiles, dyes, coatings, explosives, plastics, adhesives, and cleansers not found in natural sources.

Friedrich Wöhler has been credited with the demise of the vital force theory, thanks to his synthesis in 1828 of urea, $\text{CO}(\text{NH}_2)_2$, from ammonium sulfate and lead cyanate. Although Wöhler thus prepared an organic compound outside a living organism, he had not shown to the satisfaction of some of his contemporaries that no vital force was carried along from the organic sources of his raw materials.

Other chemical historians assign to Hermann Kolbe, who with Edward Frankland in 1845 prepared acetic acid from potassium hydroxide and acetonitrile, CH_3CN , the credit for disproving the vital force theory. However, the real conquest of the vital force theory came through a wider understanding of the true nature of organic compounds and the reasons for their behavior.

Today the term biochemistry is applied to the chemistry of living organisms. The term organic continued to be cherished, however, because compounds with a carbon framework did not seem to behave according to the valence and affinity rules which applied to inorganic compounds. By the time August Kekulé had developed structure as the clue to the anomalies of organic chemistry (1857), this had become firmly entrenched

4 NATURE AND STUDY OF ORGANIC CHEMISTRY

as a field of its own with its own language and problems. At that time organic compounds appeared to differ from inorganic in that they were more volatile, less stable to heat, slower to react, and of more complex structure.

Discovery of new organic compounds and new inorganic compounds blurred the distinctions between the two. Modern atomic theory has gone far to integrate all chemistry. Yet, it is still convenient to separate organic compounds on the basis of their very great number and close chemical relationships. Hence, organic chemistry is arbitrarily designated as the chemistry of the compounds of carbon, while inorganic chemistry claims all other compounds and the free elements. Numerous exceptions can best be learned by experience.

1-2 SUGGESTIONS FOR STUDY

However specialized a student's interest in chemistry may be later, it is essential at first for him to study the basic principles and their application in a broad area of organic reactions. Hence, a first year organic chemistry course must highlight the important representative aspects of the field.

The only satisfactory method for learning organic chemistry is to wear down many pencils in the writing of formulas and equations and in solving problems. This must be done in a thoughtful, questioning manner so as to learn why each fact is true, why each idea is accepted. Although certain facts must be learned, perhaps by rote memorization, before they can submit to theory, in general, a more inquiring approach is required for a mastery of the subject. Even the textbook should be approached, not only receptively, but critically. Nothing pleases the dedicated teacher more than his students' becoming mature enough to point out his errors and those in textbooks.

Assigned problems should be worked only after the proper foundation has been laid by mastering the text material. Problem working is not an end in itself, but a means for achieving better understanding of and greater familiarity with the reactions, concepts, or methods of the science.

The teacher usually tries to integrate the laboratory experience with the lecture and text material. Experimental proof of text or lecture assertions may be noted. Explanation should be attempted for the failure of any experiment to agree with the theory.

SUPPLEMENTARY READINGS

Benfey, O. T., *From Vital Force to Structural Formulas*, Houghton-Mifflin, Boston, 1964.

- "Editor's Outlook—Friedrich Wöhler" and W. H. Warren, "Contemporary Reception of Wöhler's Discovery of the Synthesis of Urea," *J. Chem. Educ.*, **5**, 1537-1553 (1928).
- "Justus Liebig and Friedrich Wöhler," in L. A. Goldblatt, Ed., *Readings in Elementary Organic Chemistry*, Appleton-Century, New York, 1938, pp. 9-10.
- Lipman, T. O., "Wöhler's Preparation of Urea and the Fate of Vitalism," *J. Chem. Educ.*, **41**, 452-458 (1964).
- Oesper, R. E., "Justus von Liebig—Student and Teacher," *J. Chem. Educ.*, **4**, 1461-1476 (1927).

QUESTIONS AND PROBLEMS

1. What is the modern significance of the words *organic chemistry*?
2. How did the term organic chemistry originate?
3. What contribution did Wöhler make to the early development of thought in organic chemistry? Kolbe?
4. After reading either "Justus Liebig and Friedrich Wöhler" or the articles by Lipman and Oesper, cited above, write a short paper describing the joint influence of Wöhler and Liebig on the early progress of chemistry.

2

Molecular Weights

2-1 DETERMINATION OF MOLECULAR WEIGHTS

Empirical formulas, much used in inorganic chemistry, can be calculated from the analysis of a compound. However, the nature of the carbon atom engenders too many compounds with the same empirical formula to make this of much use in organic chemistry. Before a molecular formula can be assigned to a compound, the relative molecular weight of the compound must be known.

Compounds with same empirical unit, CH_2O , but different molecular units

CH_2O	$\text{C}_2\text{H}_4\text{O}_2$	$\text{C}_4\text{H}_8\text{O}_4$	$\text{C}_6\text{H}_{12}\text{O}_6$
Formaldehyde	Acetic Acid	Methyl Glycerate	Glucose

2-2 MOLECULAR WEIGHT FROM VAPOR DENSITY

Methods developed by J. B. A. Dumas (1826) and Victor Meyer (1878), based on Avogadro's law and the common gas laws, are used to determine molecular weights of gases and vapors. An amount of volatile compound is weighed, then vaporized. The volume occupied by the compound in the vapor state is reduced to standard conditions. See a general chemistry textbook for examples.

2-3 MOLECULAR WEIGHT FROM FREEZING AND BOILING POINTS

Molecular weights of nonvolatile organic compounds are determined by applications of Raoult's law (1888) of solutions. The lowering of the vapor pressure of a solvent by a nonvolatile solute is directly proportional to the fraction of the molecules belonging to the solute (mole fraction of solute). Properties which depend on vapor pressure are boiling points, freezing points, and osmotic pressure. The effect on the first two is illustrated in the equilibrium diagram for water (Fig. 2-1).

If the concentration of solute is expressed in units proportional to mole fraction, the lowering of the freezing point or elevation of the boiling point is given by a constant multiplied by the concentration of solute. The molecular weight of solute is thus given by eq. (1)

$$(1) \quad M = \frac{1000KW}{(T_m - T_0)G}$$

where M is the molecular weight, K the molal freezing point constant or boiling point constant, W the weight of solute in grams, G the weight of solvent in grams, T_m the observed freezing (or melting) point or boiling point of the mixture, and T_0 the freezing (or melting) point or boiling point of the pure solvent.¹ The value of K depends on the solvent chosen.

¹ By Raoult's law,

$$p = p_0 x_s \quad \text{or} \quad p = p_0(1 - x_d) = p_0 - p_0 x_d$$

in which p = vapor pressure of the solution and p_0 = vapor pressure of pure solute at some temperature, T_1 ; x_s = mole fraction of solvent = $1 - x_d$ in a binary solution in which x_d is the mole fraction of solute. The equation can be solved for the difference in vapor pressure at T_1 between solution and pure solute.

$$p_0 - p = p_0 x_d$$

Over a *small* change of vapor pressure at a given temperature, T_1 , from Fig. 2-1 it can be seen that the change in boiling point or freezing point at a given pressure (e.g., atmospheric) is proportional to the change in vapor pressure at T_1 .

$$T_m - T_0 = k(p_0 - p)$$

in which T_m is the boiling point or freezing point of the solution, T_0 the boiling point or freezing point of solute, and k the corresponding constant. Thus, for relatively dilute solutions in which $p_0 - p$ is small,

$$T_m - T_0 = k p_0 x_d$$

However, it is more common to express the concentrations of such solutions in molality, that is, moles of solute per 1000 g. of solvent. Again, for low concentrations of solution, molality, m , is proportional to x_d .

$$x_d = \frac{W/M}{(W/M) + (G/M_s)} = \frac{WM_s}{W + MG} \sim \frac{WM_s}{MG}$$

when W is small. In these relationships, W = weight of solute in grams, G = weight of solvent in grams, M = molecular weight of solute, and M_s = molecular weight of solvent. By definition,

$$m = \frac{1000 W}{MG} \sim \frac{1000 x_d}{M_s}$$

when W (and thus m and x_d) are small; $1000/M_s$ is a constant for a given solvent. Substituting m for x_d , and k' for k to absorb the proportionality constant $1000/M_s$,

$$T_m - T_0 = k' p_0 m = Km$$

since p_0 is also constant for a given solvent. Substitution of its defined value, above, for m gives

$$T_m - T_0 = 1000 KW/MG$$

rearrangement of which to solve for molecular weight results in eq. (1).

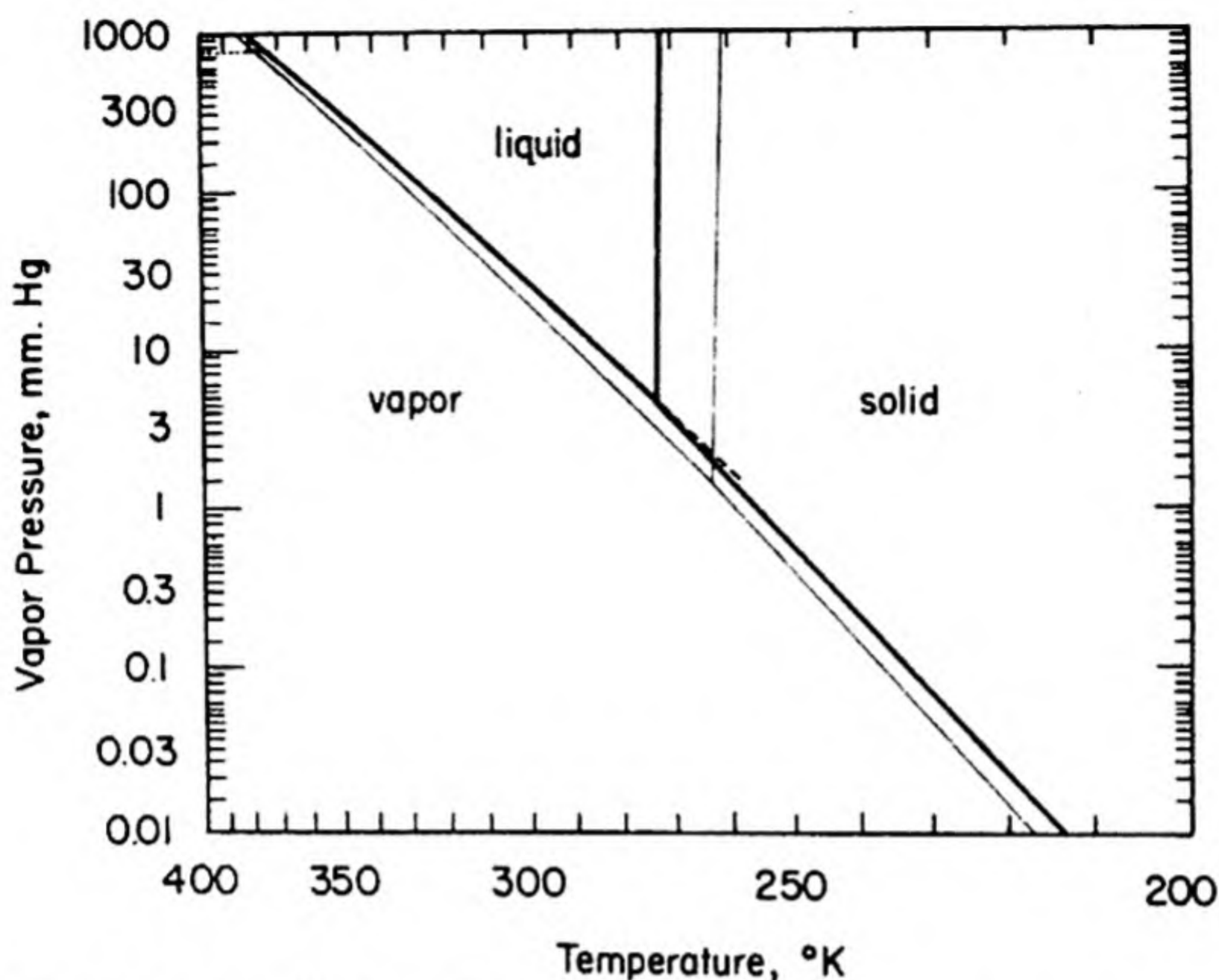


Fig. 2-1. Equilibrium Diagram of Water. Heavy lines, pure water. Light lines, water with added solute.

Cryoscopic (f.p.) constants are -1.86° for water, -37.7° for camphor.² Ebullioscopic (b.p.) constants are 0.512° for water, 6.23° for benzene.

Very accurate thermometers often must be used to measure the difference between the temperature of the pure solvent and that of the solution. One device that can measure such differences to a thousandth of a degree is the differential thermometer, one type of which is shown in Fig. 2-2. The thermometer can be set to read in any desired five-degree temperature range by trapping part of the mercury in the loop of the setting device, *a*. The very large mercury reservoir, *b*, and the very fine stem then assure high sensitivity in measuring temperature differences. Organic compounds insoluble in water may be studied in such organic solvents as benzene or camphor.

The most accurate determinations of molecular weight are obtained by measuring three values at different concentrations and extending a line graphically to the value at infinite dilution (zero concentration).

The osmotic pressure of a solution as concentrated as one molal is so enormous that this property is seldom used to determine molecular weights of ordinary substances. For compounds made up of molecules with relative weights over 10,000, however, a weighable amount of material produces a solution dilute enough for easy measurement of osmotic

² Unless otherwise indicated, temperatures are in $^{\circ}\text{C}$.

Fig. 2-2. Beckmann Differential Thermometer. (a) Setting device, (b) Bulb.



pressure. This is fortunate, for the same solutions are too dilute to give measurable temperature differences by either cryoscopic or ebullioscopic methods.

Osmotic pressure is equal to the minimum pressure required to prevent pure solvent from passing through a membrane into a solution prepared with the same solvent. The membrane must be semipermeable; that is, it must allow solvent molecules to pass, but not solute molecules.

Other methods are used to estimate molecular weights of colloidal materials (high polymers, such as starches, proteins, or synthetic resins). Some are those based on sedimentation rate, the rate of settling of the material in the strong centripetal field of an ultracentrifuge; on viscosity, the effect of large molecules on the rate of flow of a solution in a standard instrument; and on light scattering.

2-4 MOLECULAR WEIGHTS FROM OTHER PHYSICAL PROPERTIES

The mass spectrometer enables one to determine molecular weights with great accuracy up to about molecular weight 500. This is described

in Chapter 37. Spectroscopic data occasionally can be used to determine molecular weights. Nuclear magnetic resonance (Chapter 34) and X-ray diffraction (Chapter 36) have been so used.

QUESTIONS AND PROBLEMS

1. Describe the methods used to determine molecular weights of ordinary substances. State the laws upon which these depend.

2. What method can be used to determine molecular weights of compounds composed of very large molecules?

3. A sample of a volatile liquid weighing 2.588 g. was found to occupy a volume of 521 ml. at 100° and 750 mm. Calculate the molecular weight of the compound.

4. A sample of 0.0889 g. of a compound fused with 1.0352 g. of camphor melted at 148° . A sample of pure camphor melted at 173° on the same apparatus. Calculate the molecular weight of the compound.

5. When 0.2672 g. of a compound was dissolved in 10.00 g. of benzene, a boiling point of 80.70° at 760 mm. was observed. What was the molecular weight of the substance? Pure benzene boils at 80.15° at 760 mm.

3

Formulation

3-1 DETERMINATION OF COMPOSITION OF CARBON COMPOUNDS

Rarely is it necessary to analyze organic compounds quantitatively for all the elements present. In fact, reliable methods for the determination of oxygen have been developed only recently. Nevertheless, the whole scheme of organic formulas depends ultimately on analysis for the elements and knowledge of the compositions of compounds.

A. Qualitative Analysis for the Elements

Methods for detection of the elements present in organic compounds must include as the first step destruction of the covalent organic structure and formation of products for which standard inorganic analytical methods are available.

The organic nature of many compounds can be shown by their flammability, if they are volatile, or their charring to black residues if they are nonvolatile. Sooty flames and black char are evidence for carbon. More reliable is the decomposition of the compound with cupric oxide. The carbon dioxide produced precipitates calcium carbonate from a limewater solution.

B. Analysis for Carbon and Hydrogen

Carbon-hydrogen analysis is the most fundamental quantitative organic analysis. The principles involved were developed by Lavoisier in the eighteenth century. Later Justus von Liebig recast the apparatus essentially into its modern form, with the extravagant claim that he had so simplified the procedure that the analysis could be performed by any intelligent monkey. There are, however, many students who, after experience with the method, concede that if this is true, evolution should have stopped with monkeys. Because of scarcity or cost of materials, micro techniques, first developed by Fritz Pregl in 1910, are most popular. The apparatus is sketched in Fig. 3-1.

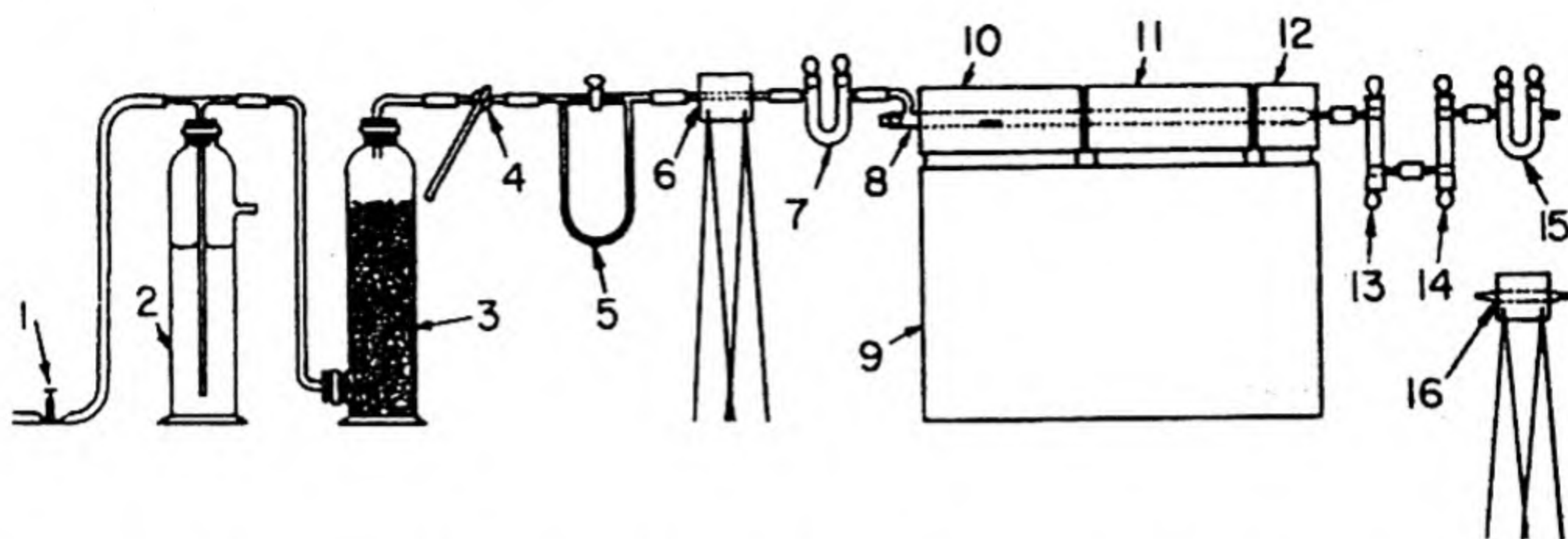
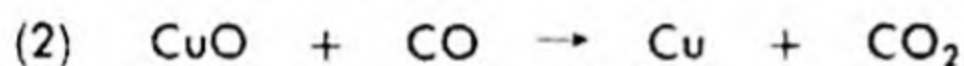
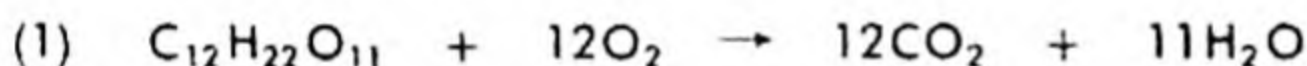


Fig. 3-1. Carbon-Hydrogen Combustion Apparatus. (1) Pinch clamp, (2) Pressure regulator, (3) Drying tower, (4) Flow regulator, (5) Capillary flowmeter, (6) Electric preheater, (7) Final O₂ purifier, (8) Combustion tube, (9) Furnace controls, (10) Sample heater, (11) Combustion furnace, (12) Plug heater, (13) Water absorption tube, (14) CO₂ absorption tube, (15) Guard tube, (16) Hopcalite tube and electric heater used between 13 and 14 when nitrogen is present. (Hopcalite is a mixture of CuO, CoO, MnO₂, and Ag₂O.)

The sample is burned in a stream of oxygen to oxides of carbon and to water. Cupric oxide is used in the combustion tube (Fig. 3-2) to insure the conversion of carbon monoxide to carbon dioxide. See eqs. (1) and (2) for the combustion of sucrose (cane sugar).



The gain in weight of the absorption tubes, containing materials suitable for absorbing water and carbon dioxide, respectively, represents the amount of oxidized hydrogen and carbon in the original organic compound. Alternatively, the product gases can be analyzed by vapor phase chromatography.

If, as is usually the case for the product of a synthesis, the investigator anticipates the composition of the product, he compares the result of analysis with the composition calculated for the expected product. Suppose that the product may be C₇H₆O₃. If the analysis agrees with the

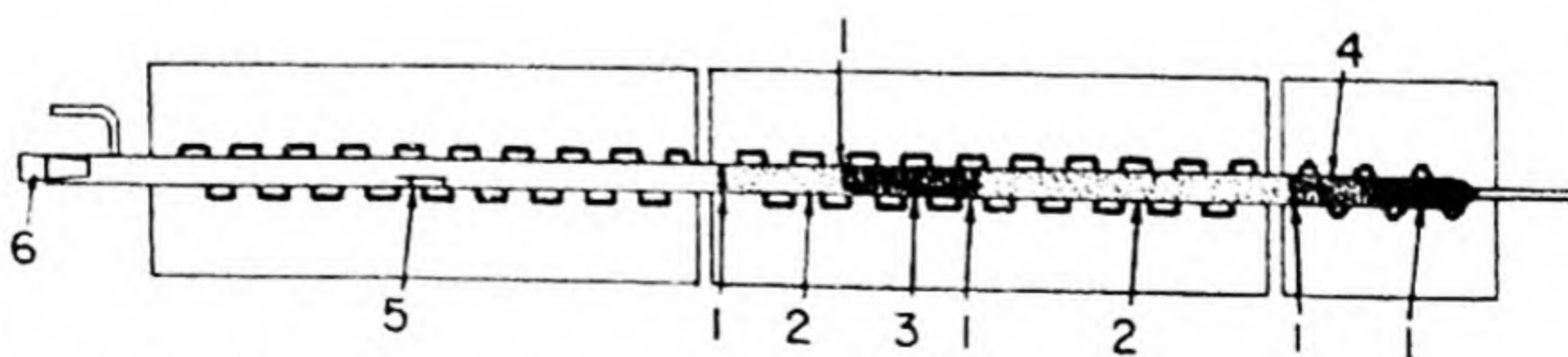
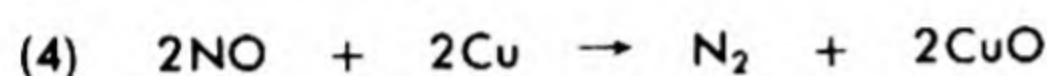
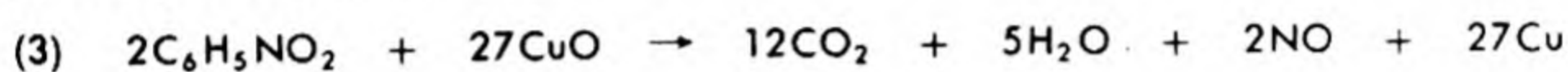


Fig. 3-2. The Combustion Tube. (1) Silver wool plug, (2) Copper chromite on emery, (3) Cupric oxide wire, (4) Emery, (5) Boat containing sample, (6) Tight-fitting inert stopper.

calculated composition for the compound, it would be reported thus: Calculated for $C_7H_6O_3$: C = 60.87%; H = 4.35%. Found: C = 60.93%; H = 4.32%.

C. Analysis for Nitrogen

The two methods now used to determine nitrogen are the Dumas gasometric method (1830) and the Kjeldahl titrimetric method. The Dumas train is shown in Fig. 3-3. The sample is oxidized by cupric oxide, which produces nitrogen and its oxides. The oxides are reduced to nitrogen by hot copper gauze. The resulting gases are then swept into the azotometer, where the volume of nitrogen is measured over a concentrated potassium hydroxide solution.



In the Kjeldahl procedure, a sample is digested with concentrated sulfuric acid, potassium sulfate, and a catalyst. The resulting ammonium sulfate is converted to ammonia by addition of sodium hydroxide. The ammonia is distilled into a measured volume of standard acid, which is titrated with standardized base to determine the quantity of ammonia.

The Kjeldahl method is used mainly for the analysis of foods and agricultural products. The Dumas method is generally used for pure compounds. However, recent micro-Kjeldahl techniques have made this method more attractive to investigators who have only small samples for analysis.

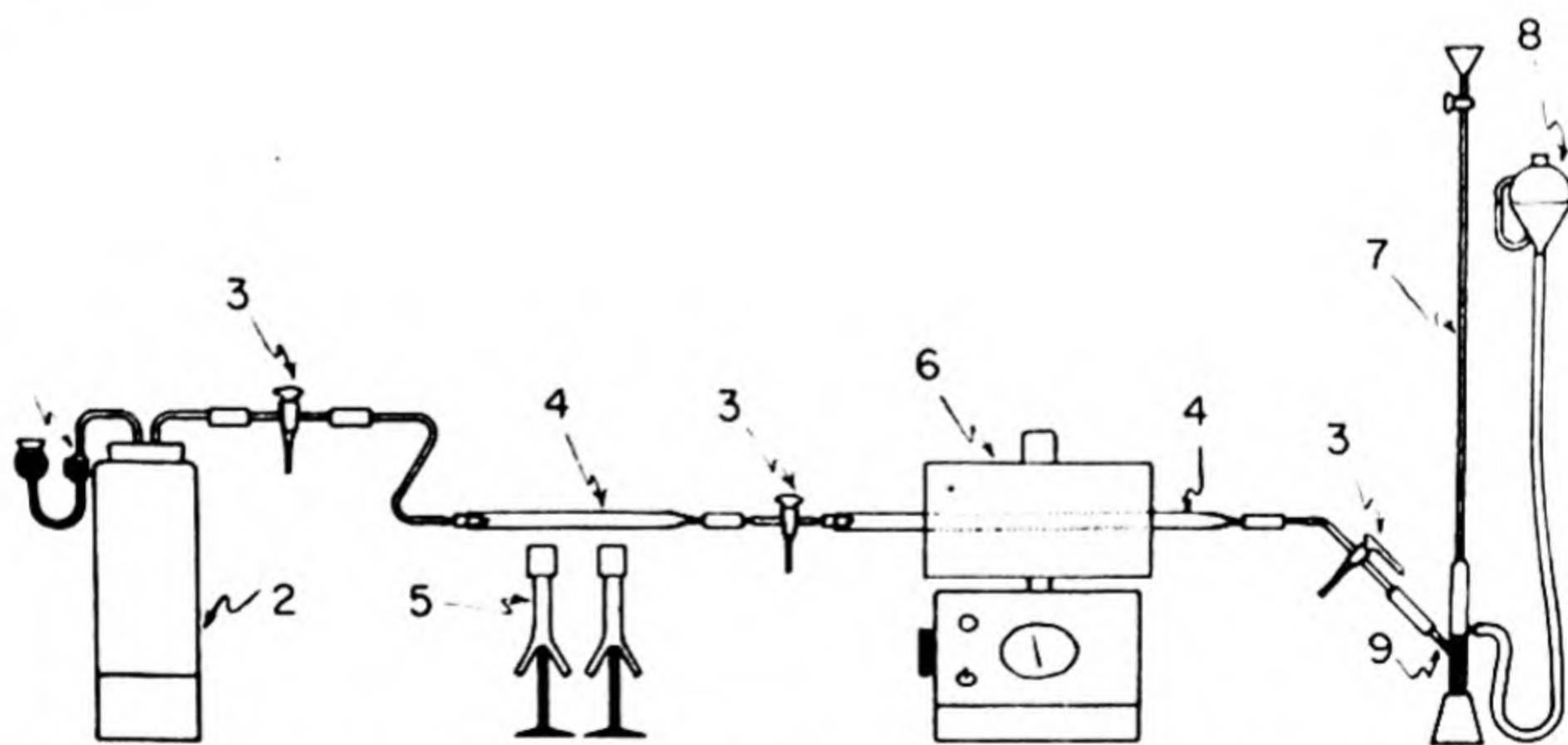


Fig. 3-3. Dumas Nitrogen Train. (1) Mercury pressure regulator, (2) Vacuum bottle containing solid CO_2 , (3) Three-way stopcock, (4) Combustion tube, (5) Burners, (6) Combustion furnace, (7) Schiff azotometer, (8) Leveling bottle, (9) Mercury seal and blowoff valve. (Modification of Shelberg, *Anal. Chem.* **23**, 1492-1493 (1951), used by permission of Dr. Shelberg and the publisher.)

3-2 FORMULAS, STRUCTURES, AND CONFIGURATIONS

A. Empirical and Molecular Formulas

As was pointed out in §2-1, the empirical formula is inadequate for the variety of compounds in organic chemistry. Application of physical laws discussed in §2-2 and §2-3 lead to molecular weights. Multiplication of the empirical formula by a suitable small integer gives a formula in which the sum of atomic masses equals the molecular weight. This is a molecular formula.

B. Structures

Even molecular formulas fall short of the needs of the organic chemist in representing compounds. The five simplest hydrocarbons of the paraffin series are methane, CH_4 ; ethane, C_2H_6 ; propane, C_3H_8 ; and two

TABLE 3-1. Formulas and Structures of Some Hydrocarbons

Compound	Molecular Formula	Structural Formula
Methane	CH_4	$\begin{array}{c} \text{H} \\ \\ \text{H}-\text{C}-\text{H} \\ \\ \text{H} \end{array}$
Ethane	C_2H_6	$\begin{array}{cc} \text{H} & \text{H} \\ & \\ \text{H}-\text{C} & -\text{C}-\text{H} \\ & \\ \text{H} & \text{H} \end{array}$
Propane	C_3H_8	$\begin{array}{ccc} \text{H} & \text{H} & \text{H} \\ & & \\ \text{H}-\text{C} & -\text{C} & -\text{C}-\text{H} \\ & & \\ \text{H} & \text{H} & \text{H} \end{array}$
<i>n</i> -Butane	C_4H_{10}	$\begin{array}{cccc} \text{H} & \text{H} & \text{H} & \text{H} \\ & & & \\ \text{H}-\text{C} & -\text{C} & -\text{C} & -\text{C}-\text{H} \\ & & & \\ \text{H} & \text{H} & \text{H} & \text{H} \end{array}$
Isobutane	C_4H_{10}	$\begin{array}{ccc} \text{H} & \text{H} & \text{H} \\ & & \\ \text{H}-\text{C} & -\text{C} & -\text{C}-\text{H} \\ & & \\ \text{H} & \text{H}-\text{C}-\text{H} \\ & \\ & \text{H} \end{array}$

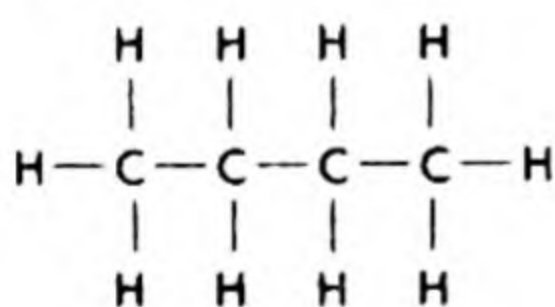
butanes, both with the molecular formula C_4H_{10} . All of these compounds have similar properties, despite apparent formula differences. In CH_4 , carbon has a valence of four; in C_2H_6 , apparently three. In C_3H_8 , the valence of carbon appears to be $2\frac{2}{3}$. Early chemists could not explain such apparently fractional valences. Two distinct compounds corresponding to C_4H_{10} further complicate the situation. Primitive valence rules and molecular formulas provide no explanation for these anomalies.

Friedrich August Kekulé first solved the problem in 1857 by proposing to represent molecules by pictures or graphs showing the connections between atoms, with the postulate that carbon atoms can be connected to

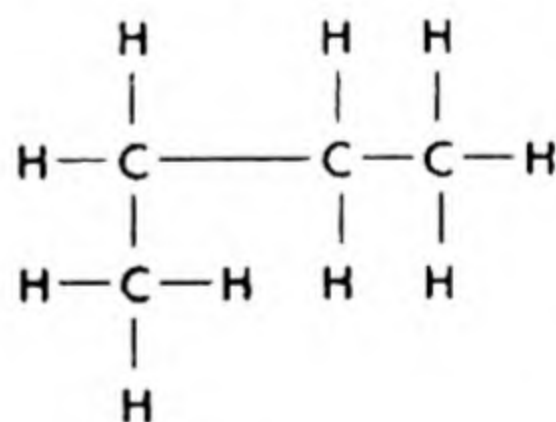
each other. CH_4 becomes $\begin{array}{c} H \\ | \\ H-C-H \\ | \\ H \end{array}$. These graphs are called *structural*

formulas. Others are given in Table 3-1. The two structures for C_4H_{10} explain the existence of two butanes. The connections between carbon atoms explain the maintenance of the tetravalence of carbon in spite of the anomalous valences seemingly present in the molecular formulas.

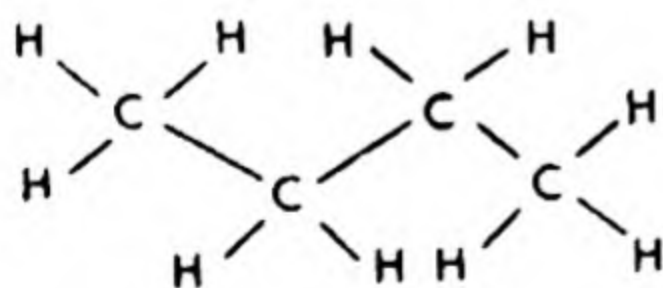
It cannot be overemphasized that the structural formula of a molecule does not in any way represent a spatial picture of a molecule any more than a road map represents the contours of the terrain. Molecules exist in three dimensions, whereas their structural formulas are drawn in two. A structural formula shows only the order of connection of atoms in a molecule. The formulas I-V all represent the same structure, that of *n*-butane (normal butane). They all show four carbon atoms connected in



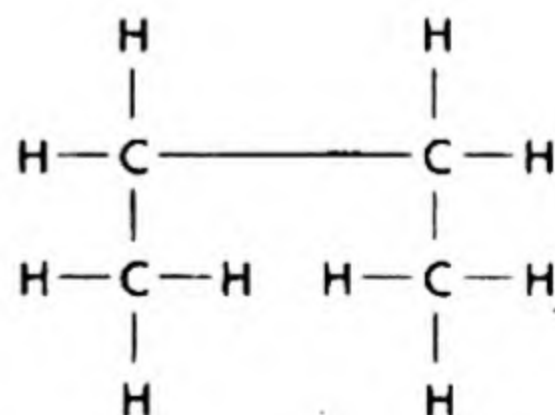
I



II



III



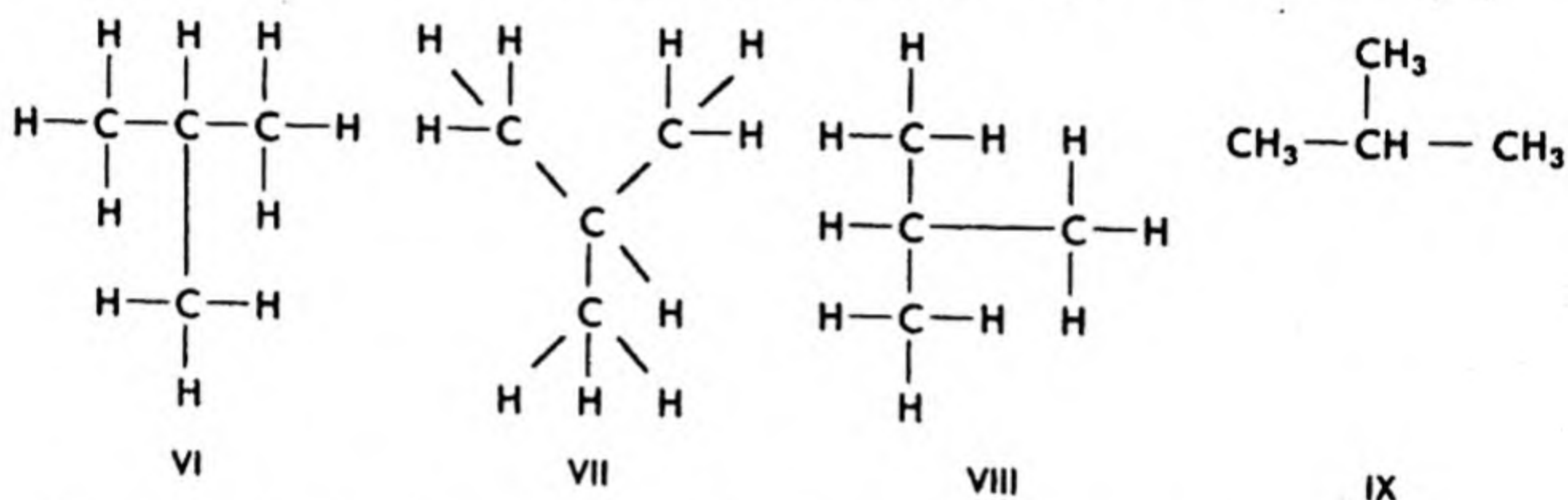
IV



V

sequence in a continuous chain, with three hydrogen atoms connected to each of the two terminal carbon atoms, and two hydrogen atoms connected to each of the two inner carbon atoms.

On the other hand, all of the structural formulas of isobutane, VI-IX, are different from the formulas above, but all represent the same molecule. Here three carbon atoms are connected to the same central carbon atom, which in turn is connected to but one hydrogen atom. The other three carbon atoms each hold three hydrogen atoms. The two structures and the compounds they represent, which have the same molecular formula, are called *isomers*. Some models are shown in Figs. 3-4 and 3-5.



To maintain the tetravalence of carbon and univalence of hydrogen in compounds such as ethylene, X, and propylene, XI, it is necessary to con-

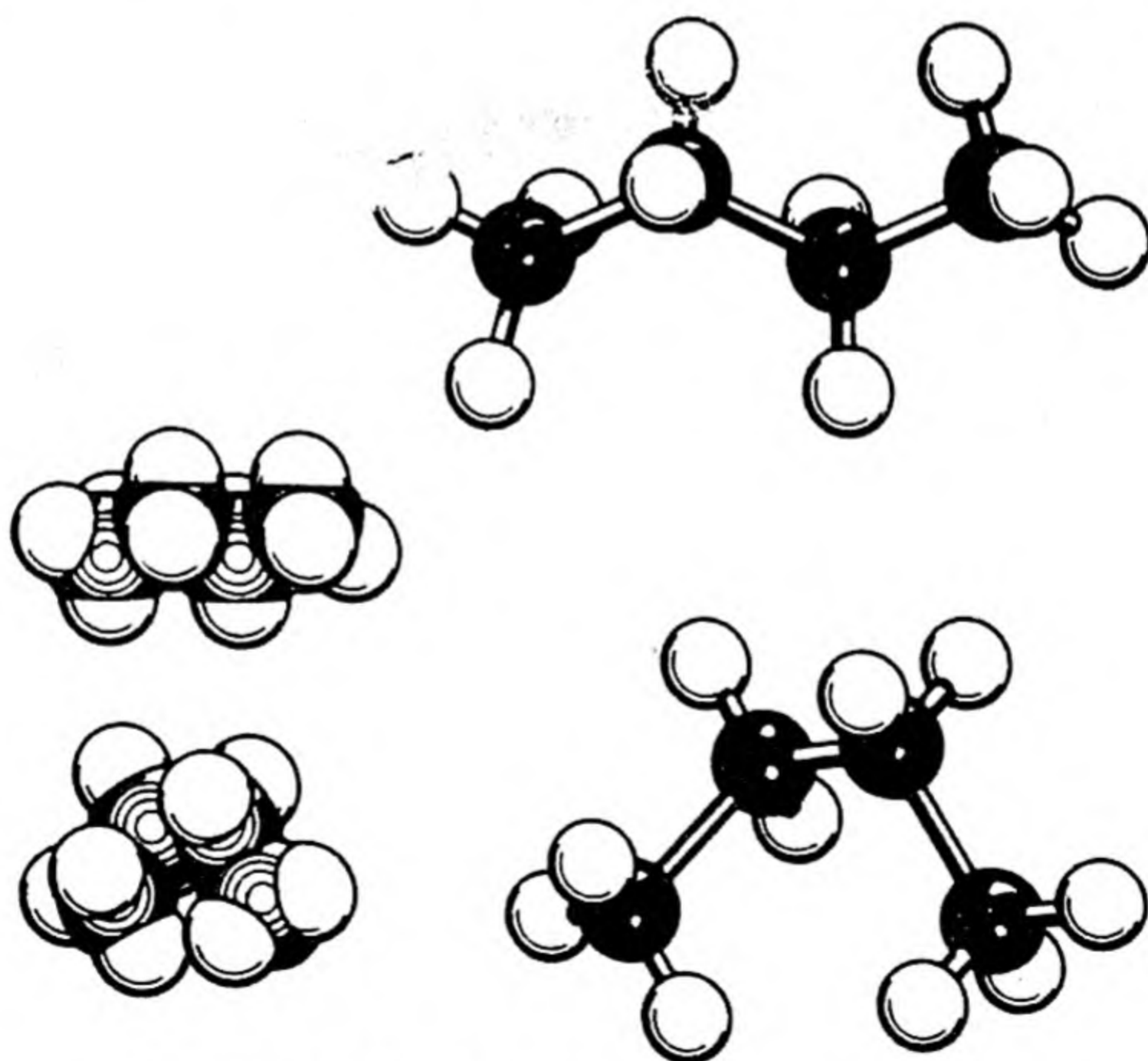


Fig. 3-4. Molecular Models of Normal Butane.

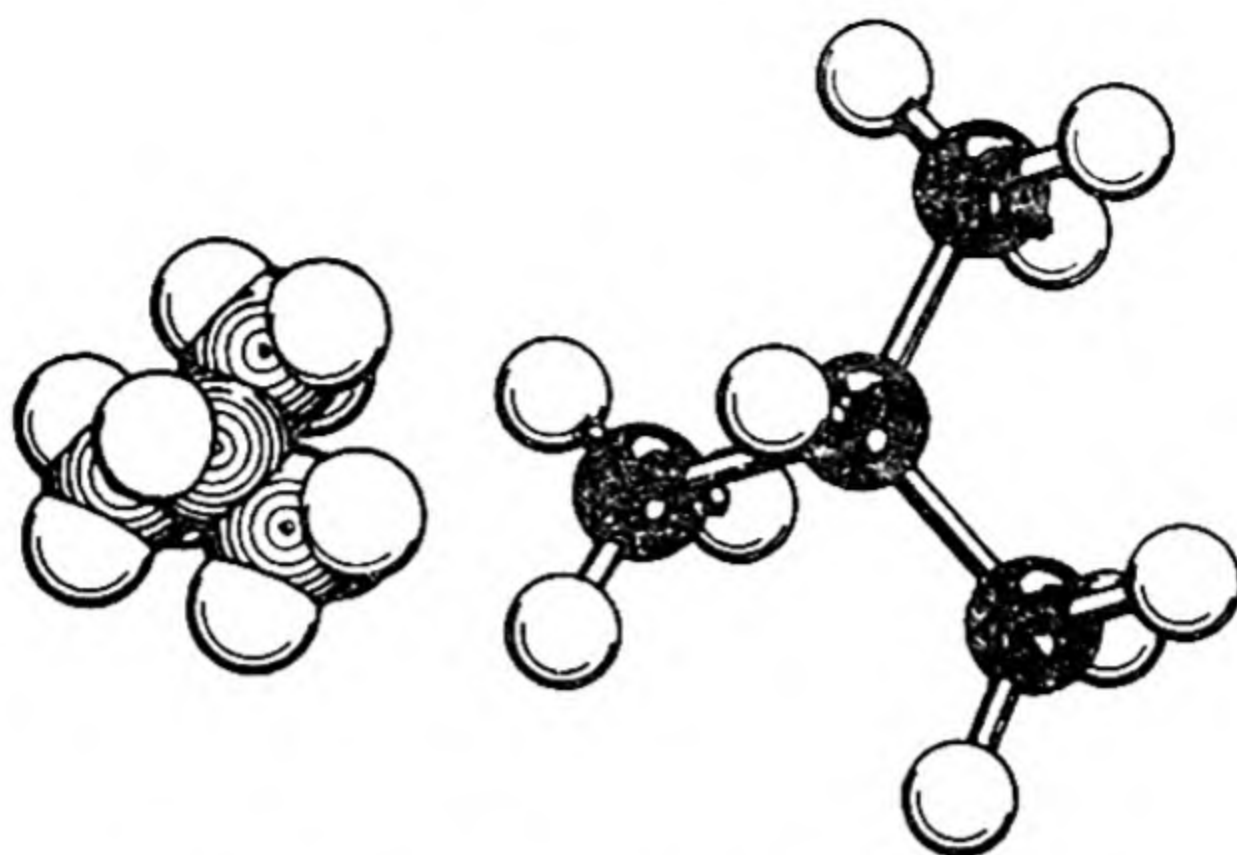
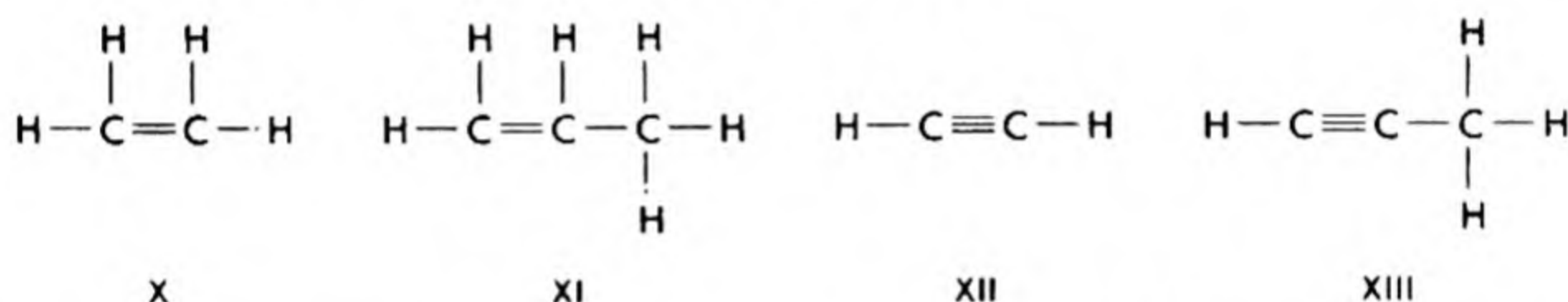


Fig. 3-5. Molecular Models of Isobutane.

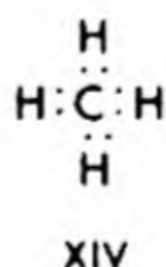
sider two valences of one carbon atom united with two valences of the other. Bonds so formed are called double bonds.



Similarly, acetylene, XII, and methylacetylene, XIII, are said to have triple bonds.

C. Electronic Formulas

With the modern electron theory of matter came a reinvestigation of the connections between atoms. It was found that structures of molecules could be interpreted in terms of electron pair bonds between atoms. A single bond represents one shared pair of electrons; a double bond, two shared pairs of electrons; a triple bond, three shared pairs. Thus, methane is represented electronically according to formula XIV. In an electronic



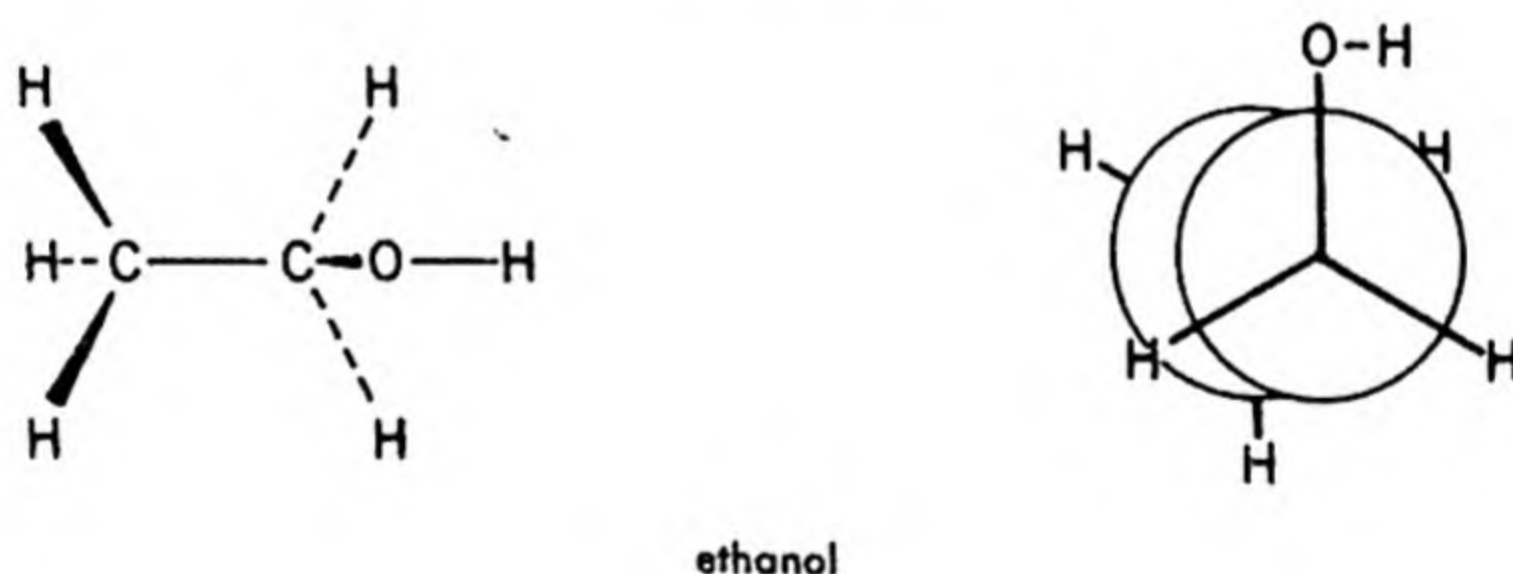
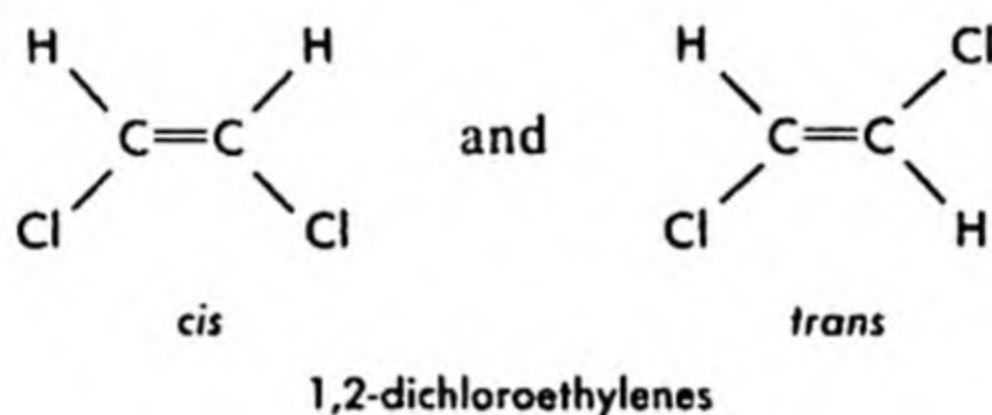
formula, the elementary symbol represents the kernel of an atom, and each dot a shared or unshared electron in the valence level of the atom. (The kernel of an atom is the atom less its valence electrons.) Like structural formulas, electronic formulas give no clue as to the spatial arrangement of the atoms or to the behavior of the bonding electrons. Nothing is

implied about how the electrons hold the atoms together or where they are placed in the molecule.

D. Configurations and Conformations

It is often helpful to consider the spatial arrangement of molecules and to represent them as three-dimensional entities. The arrangement in space of the atoms in a molecule is the configuration or conformation of the molecule. A configurational or conformational formula is a two-dimensional projection used to represent molecular configuration or conformation. *Configuration* designates a spatial arrangement that is stable and produces separable spatial isomers. *Conformation* designates a momentary or passing geometrical arrangement that is too readily converted to a different conformation for geometrical isomers to be isolated.

Thus, the two isomers of 1,2-dichloroethylene below are separable configurations, whereas the formulas for ethanol represent the same temporary conformation.



QUESTIONS AND PROBLEMS

1. What information can be gained from the quantitative analysis of a compound? From its molecular weight in addition to its composition?
2. Define and illustrate the following terms:
 - a. molecular formula
 - b. structure
 - c. electronic formula
 - d. molecular configuration
3. Draw the electronic formula of each of the following compounds and show the types of valence found in each:
 - a. ammonia
 - b. ammonium chloride
 - c. methane

4. Write structures and electronic formulas for substances which contain double bonds; triple bonds. Do these substances have any single bonds? Label the types of bonds in the formulas.

5. The analysis of a compound having a molecular weight of 84 gave the following data:

Tared boat + sample	0.15881 g.
Tared boat, empty	0.14869 g.
Tared water absorption tube, after combustion	0.10294 g.
Tared water absorption tube, before combustion	0.08987 g.
Tared carbon dioxide absorption tube, after combustion	0.47699 g.
Tared carbon dioxide absorption tube, before combustion	0.44521 g.

Calculate the per cent of carbon and hydrogen in the compound, and calculate its molecular formula.

6. From the following data, deduce the structure of an organic compound:

Analysis: C = 79.88%, H = 20.12%

Volume of 0.152 g. of the compound at 0° and 760 mm. is 112 ml.

Use valence rules to aid in getting the structure from the molecular formula.

7. From the following data, deduce the structure of an organic compound:

Analysis: C = 37.2%, H = 7.8%

Volume of 2.00 g. of the compound at 20° and 760 mm. is 747 ml.

The compound gives a positive Beilstein test, indicating the presence of halogen.

Use valence rules to aid in getting the structure from the molecular formula.

4

Bonding and Chemical Reactivity

4-1 PRINCIPLES WHICH UNDERLIE CHEMICAL BONDING

All chemical associations between atoms are the result of the necessity that those atoms achieve a state of greater stability than that of the free atoms. To learn what is most stable for an atom, we must study those elements whose atoms are notably stable and whose few chemical reactions do not change their electronic structures fundamentally. The electron configuration of an atom, and possible changes therein engendered by chemical interactions with other atoms, form the basis for all chemical activity.

A comparison of the elements helium, neon, and others in the helium group of the periodic table with stable compounds of other elements shows that elements tend to approach the electronic states of so-called noble gases nearby in atomic number, that is, by minimum expenditure of energy, to acquire electron configurations which resemble those of noble gases.

A. Atomic Structure

Principles of atomic structure, as derived from atomic spectroscopy and as described by quantum mechanics, teach that electrons are placed in atoms in discrete energy levels. Although a precise physical picture of atomic electron energy levels is unattainable, due to the Heisenberg uncertainty principle, which describes the impossibility of attaining knowledge simultaneously of both the position and the momentum of an atomic particle, a statistical picture based on the probability of location of an electron in a given volume has proved to be very useful. Such a picture is derivable from highly mathematical approaches called quantum mechanics, wave mechanics, or statistical mechanics (three mathematical systems based essentially on the same fundamental concepts.) Fortunately, it is not necessary to understand the mathematical processes to apply the conclusions.

Electrons (as well as other material bodies) have both wave properties

and particulate properties. The former are more important in a description of electronic energy states. In a given state, the probability density distribution of an electron (the probability of finding the electron in a given volume) is called the *orbital* of that electron. The shape of the orbital is defined by contour surfaces of constant probability. The electron orbital, thus described in probability terms, is like a cloud without sharp boundaries. (The probability exists whether an electron is available to fill it or not; one may speak of an empty orbital.)

The state of each electron is described by four *quantum numbers*. The *Pauli exclusion principle* states that no two electrons in the same atom can have the same four quantum numbers; at least one must differ.

The four quantum numbers describe four different properties of the electron. These are its "shell," or principal level, its angular momentum, its magnetic moment (due to its motion as a charged body), and its spin.

The constant which determines the principal energy level of an electron is the principal quantum number, n , which is any positive integer (eq. 1).

$$(1) \quad n = 1, 2, 3, \dots$$

The angular momentum constant, called the azimuthal quantum number, l , is also an integer, related to n as in eq. (2).

$$(2) \quad l = 0, 1, \dots, n - 1$$

The magnetic constant, called the magnetic quantum number, m , is an integer which is related to l as in eq. (3).

$$(3) \quad m = -l, \dots, -1, 0, +1, \dots, +l$$

The spin quantum number, s , is independent of the other three, and has either of two values, $+\frac{1}{2}$ or $-\frac{1}{2}$, depending on the direction of rotation of the electron on its axis in the atomic frame of reference.

The quantum numbers and the energies of electrons in the states described by these numbers in a typical atom are illustrated in Fig. 4-1. The energies can be calculated in principle by placing the appropriate quantum numbers in a wave equation for the given atom. The energy states are often designated by letters, as the *K* shell ($n = 1$), *L* shell ($n = 2$), *M* shell ($n = 3$), etc., and *s* electrons ($l = 0$), *p* electrons ($l = 1$), *d* electrons ($l = 2$), and *f* electrons ($l = 3$). These letters, the outgrowth of spectroscopic studies which antedated quantum theory, are used like names to designate quantum states.

The question, what electron states of an atom are most stable, can be approached empirically through a study of the periodic table and the manner in which this table depends on quantum numbers of energy states. First, the electrons of an atom in its ground, or unexcited, state must be

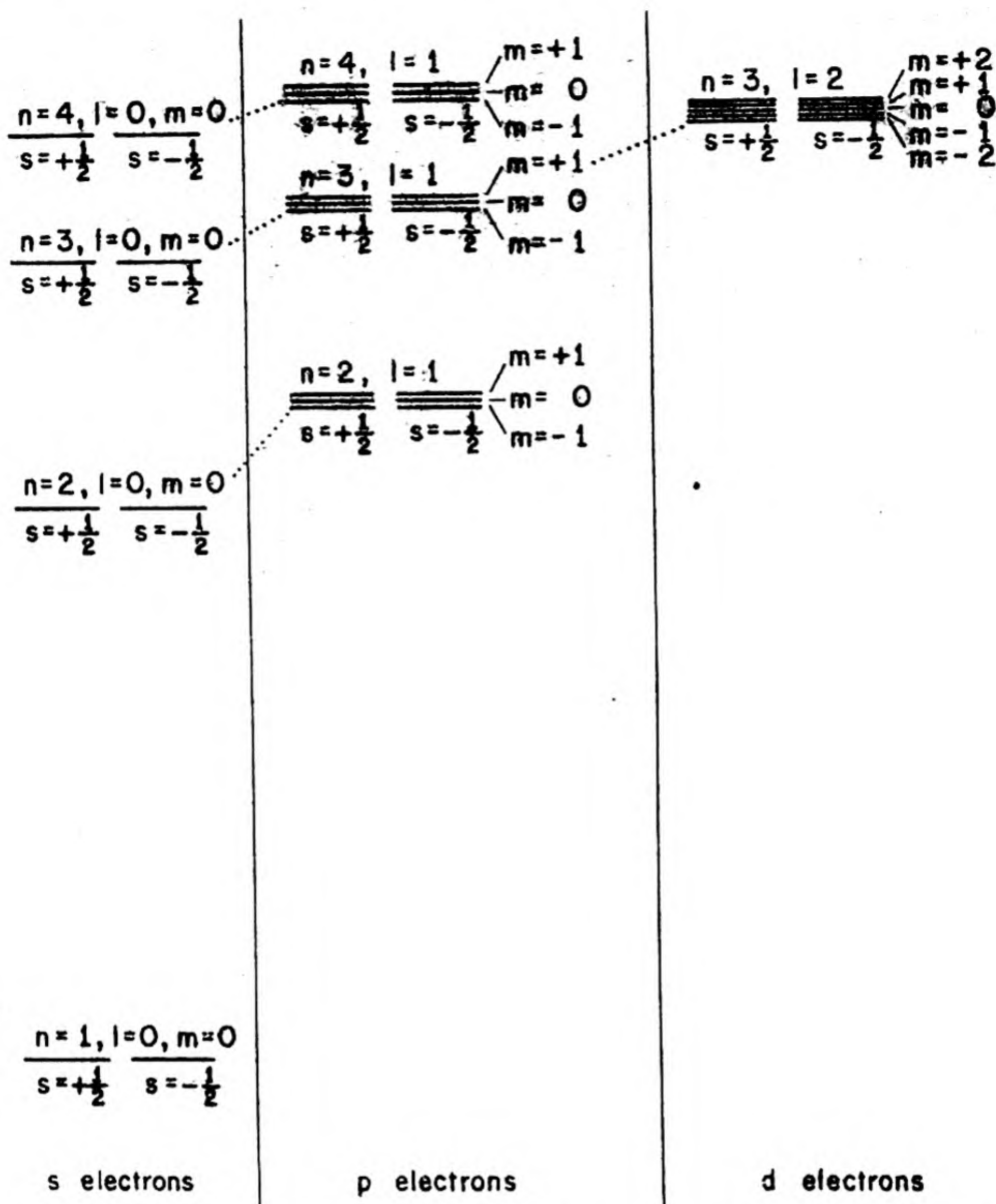


Fig. 4-1. Energy Level Representation of Quantum Numbers. Levels differing in m numbers are shown separately, although except in applied magnetic fields, these levels have the same energies (are degenerate).

in the lowest available energy levels (the aufbau principle). Otherwise, the atom could still lose energy, or become more stable, as electrons fall to lower states. Then, certain arrangements of electrons seem in themselves to be particularly stable. These occur notably in atoms at the *ends of periods* (called either Group 0 or Group 8) in the periodic table. This raises the question of how the periodicity of atomic properties depends on the number of electrons in the atom.

As atoms advance in atomic number, each added electron goes into the energy level next higher than that of the preceding electron (except that certain states are essentially equivalent in energy when not in a strong, inhomogeneous magnetic field). The first electron is in the level described as $n = 1, l = 0, m = 0, s = -\frac{1}{2}$. The second differs only in having $s = +\frac{1}{2}$.

When $n = 1$, l can only be 0, eq. (2), and m only 0, eq. (3). No more electrons can occupy the K shell. The third electron must go into the L shell, $n = 2$. This starts the second period. A new period starts when the next added electron goes into a higher shell (i.e., has a higher principal quantum number) than the last electron of the preceding element. The neutral atom with two electrons, helium, has one filled shell and is an unreactive atom.

The addition of electrons with advancing atomic number continues:

3:	$n = 2,$	$l = 0,$	$m = 0,$	$s = -\frac{1}{2}$
4:	—	—	—	$+\frac{1}{2}$
5:	—	$l = 1,$	$m = -1,$	$s = -\frac{1}{2}$
6:	—	—	0,	$-\frac{1}{2}$
7:	—	—	$+1,$	$-\frac{1}{2}$
8:	—	—	$-1,$	$+\frac{1}{2}$
9:	—	—	0,	$+\frac{1}{2}$
10:	—	—	$+1,$	$+\frac{1}{2}$

With the tenth element, once more a shell is filled. The eleventh electron goes into the M shell, $n = 3$. Like helium, the tenth element, neon, is unreactive.

The third period proceeds like the second to element 18. Then, a new factor arises (Fig. 4-2). The energy of the state $n = 4, l = 0$ is *lower* than that of the state $n = 3, l = 2$. Instead of continuing to fill its M shell, the nineteenth element (potassium) begins a new period by having its highest-energy electron in the N shell. The eighteenth element thus does not have a full outer shell, but nevertheless it is an unreactive element (argon). The remaining stable elements resemble the argon pattern. Electron configurations for those through xenon are given in Table 4-1.

TABLE 4-1. Electron Configurations of Unreactive Elements (Inert Gases)

Symbol	K shell	L shell		M shell			N shell				O shell	
		s	p	s	p	d	s	p	d	(f)	s	p
He	2	2 + 6										
Ne	2	2 + 6										
Ar	2	2 + 6		2 + 6								
Kr	2	2 + 6		2 + 6 + 10			2 + 6					
Xe	2	2 + 6		2 + 6 + 10			2 + 6 + 10				2 + 6	

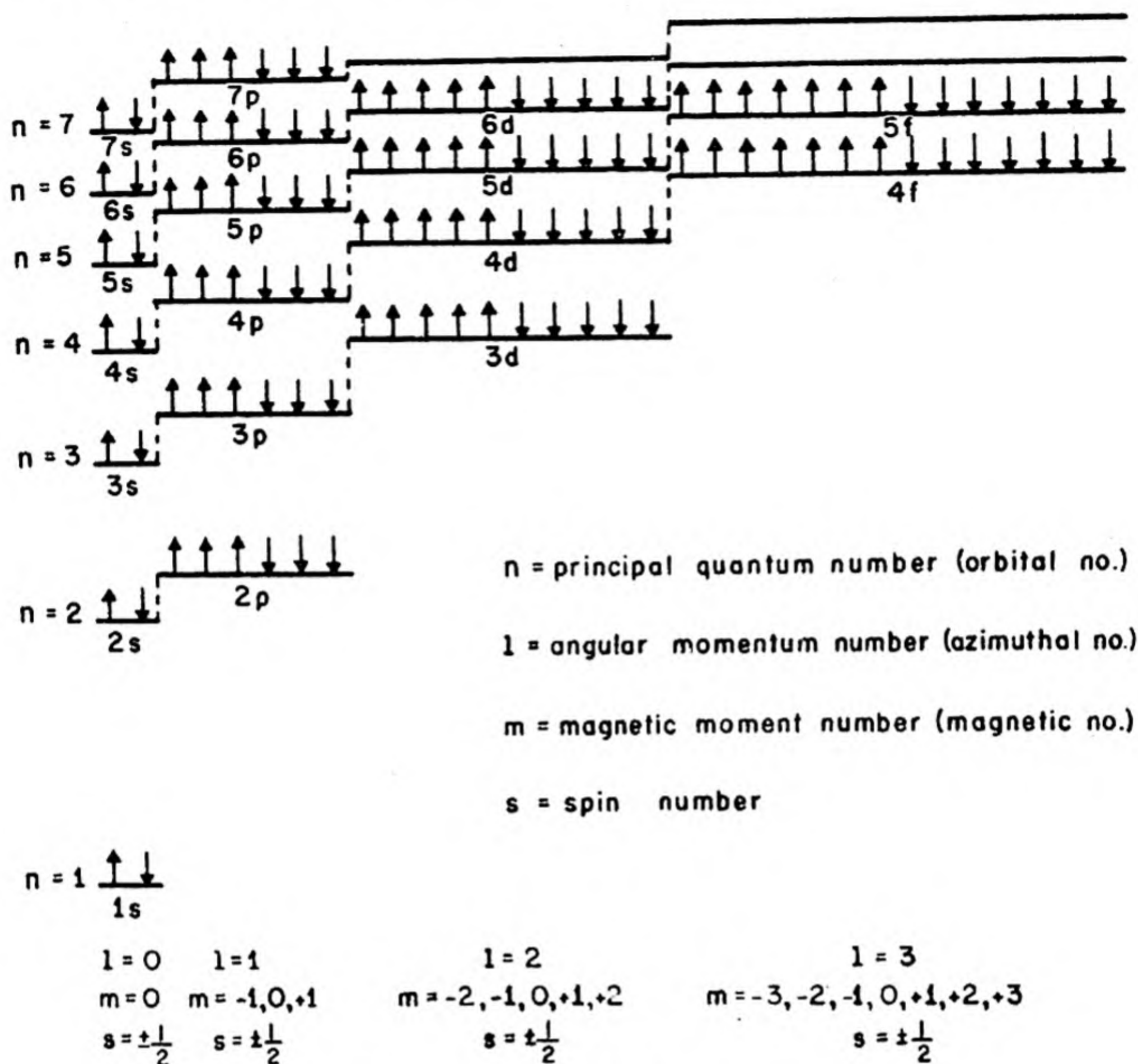
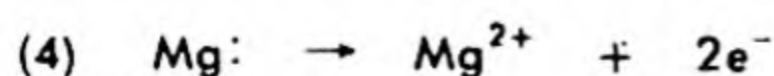


Fig. 4-2. Atomic Orbital Sublevels and Their Relative Energies.

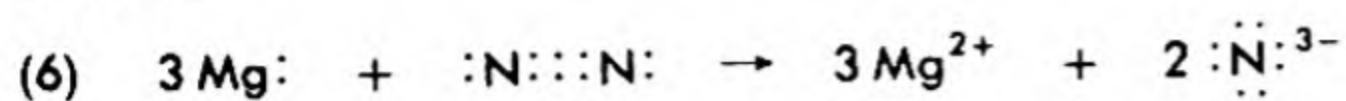
Except for helium, which has a full K shell of two electrons, all of the stable elements have two s ($l = 0$) electrons and six p ($l = 1$) electrons in their outermost levels; these are the states other atoms tend to approach by chemical reactions.

B. Electrovalence

In order to acquire inert gas configurations, some atoms are able to lose (donate) electrons, others to gain (accept) electrons. For example, magnesium and nitrogen react by electron transfer to form ions (eqs. 4 and 5). Both of the ions have the neon configuration, $1s^2 2s^2 p^6$ (which means two s electrons in the K shell, two s electrons and six p electrons in the L shell).



Overall:



The ions are held together by the electrostatic attractions due to their opposite charges. This attraction constitutes an electrovalent bond.

Those atoms not near enough to inert gas configurations to comply with the energy requirements for the formation of simple ions must achieve chemical stability by other means. They avoid charge accumulation by the sharing of electrons among two (or sometimes more) separate atomic orbitals between the connected atoms. Such sharing ties the atoms together by a covalent bond.

C. Covalent Bonding. The Hydrogen Molecule

To understand how atoms can approach inert gas stability by sharing electrons, let us consider the cases of two separate hydrogen atoms, the hydrogen molecule and the helium atom. Each separate hydrogen atom has one proton and one electron. Each conceivably may acquire a stable configuration by accepting an electron, but both atoms cannot act as acceptors without an outside donor. But, if the two atoms form an aggregate with the two protons close enough together to allow the two electrons to occupy an orbital around them, the aggregate, or molecule, has a helium-like configuration (Fig. 4-3). In helium, the electrons position

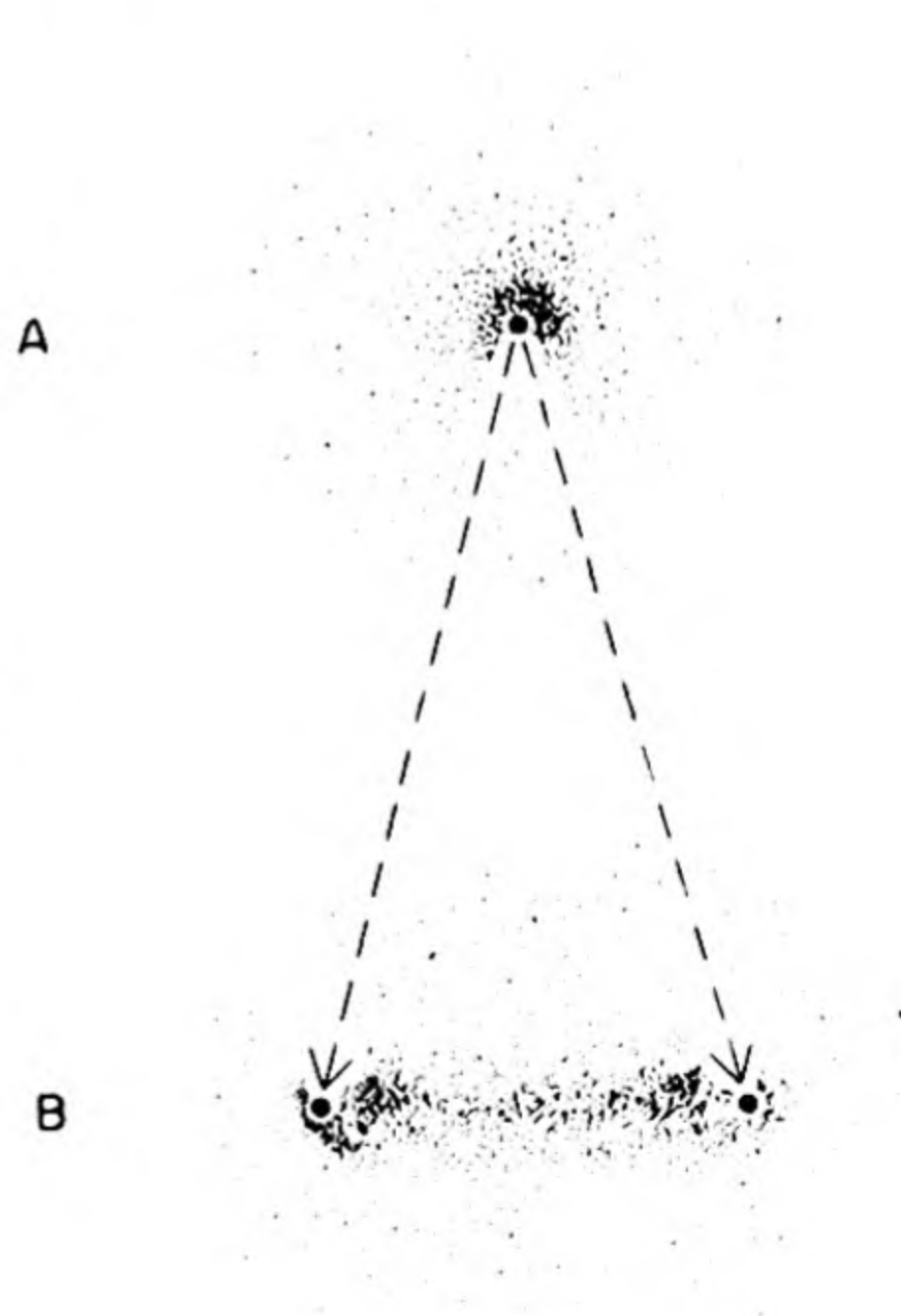


Fig. 4-3. Analogy between (A) a Helium Atom and (B) a Hydrogen Molecule.

themselves about a single, two-unit, positive charge, while in the hydrogen molecule the electrons must stretch out to position themselves about two separate atomic nuclei.

D. Bond Dissociation Energies

Let us consider what happens in terms of potential energy as two hydrogen atoms approach each other. Either of two things may occur. If the electrons of both atoms have parallel spins (both $-\frac{1}{2}$ or both $+\frac{1}{2}$), no bond can form, for then two electrons of identical quantum numbers would occupy the same orbital (violation of the Pauli exclusion principle). The closer the two nonbonding atoms approach each other, the more their nuclear charges and their valence electrons repel each other, and the higher is the potential energy of the two-atom system (Fig. 4-4A, moving to the left).

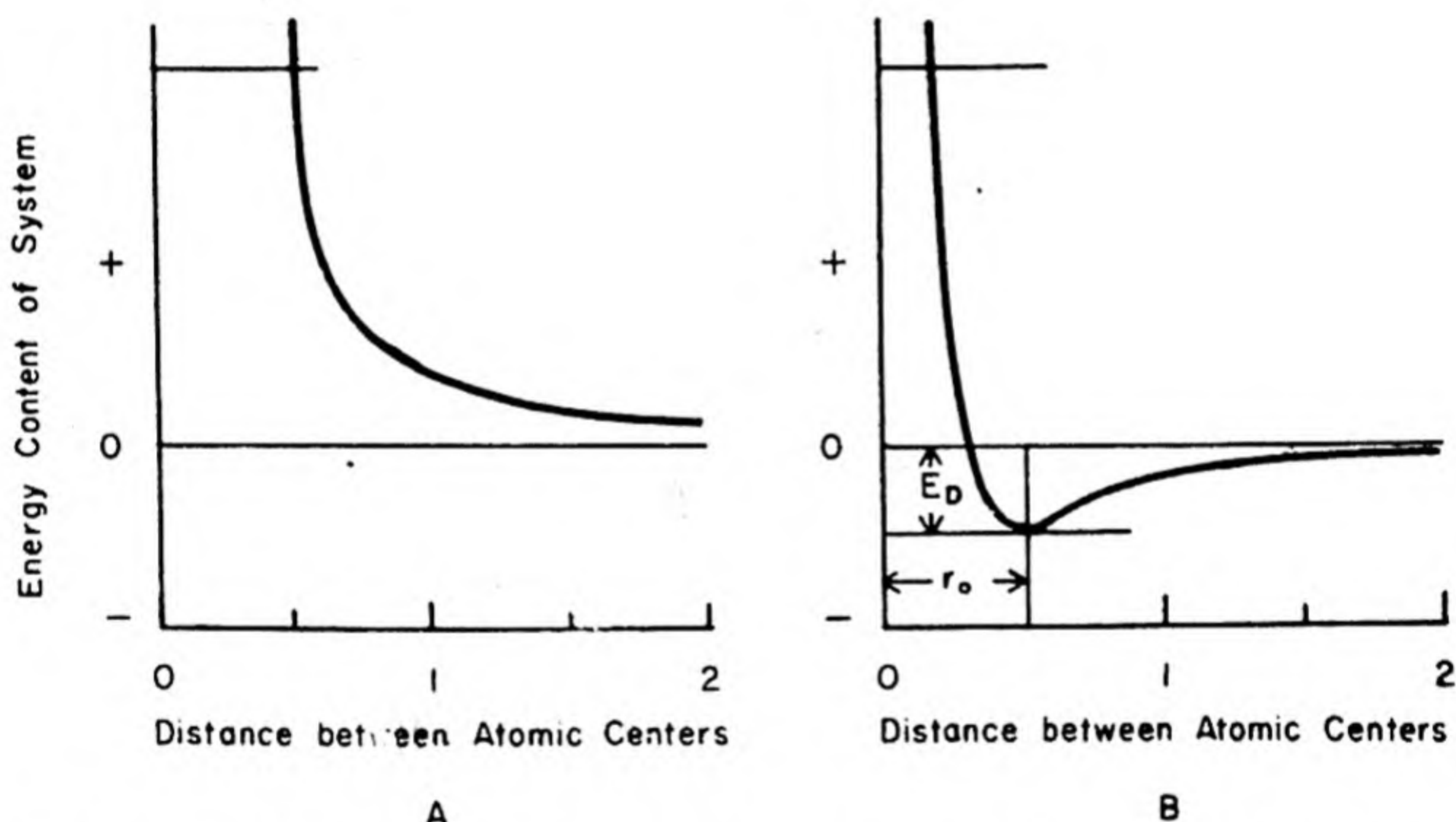


Fig. 4-4. Total Energies of Systems of Two Hydrogen Atoms. (A) Nonbonding conditions, (B) Bonding conditions. Zero energy = energy of separated atoms. r_0 = bond distance. E_D = bond dissociation energy.

Under bonding conditions (valence electrons antiparallel; one spin $-\frac{1}{2}$, the other $+\frac{1}{2}$), the spin moments of the two electrons couple, or the electrons are said to pair. This results in an attraction as the two atoms approach each other and a decrease in potential energy up to a certain distance (Fig. 4-4B, moving toward the left). At this point, r_0 in Fig. 4-4B, further repulsions between the nuclei increase the energy of the system more than electronic coupling decreases it, so that the energy of the system rises again, quite steeply, when the two atomic nuclei come closer

together than r_0 . This prevents the two hydrogen atoms from collapsing to form a ${}^2\text{He}$ atom and establishes a definite distance between the nuclei, r_0 , called the *bond distance*, at which the atoms are most stable. The energy difference between this state, at which the atoms have formed a stable molecule, and the state to the right in Fig. 4-4B, at which the atoms are separate, independent, neutral units, is called the *bond dissociation energy* of the $\text{H}:\text{H}$ bond. The exact values for the bond distance and bond dissociation energy between any two atoms in a molecule depends on the balancing of attractive and repulsive forces between parts of the molecule.

E. Covalent Bonding in More Complex Molecules

As a case typical of somewhat more complex systems, let us consider hydrogen fluoride and its relationship to neon. Only the outermost (valence) shell of electrons participates in the bonding of second and third period elements; the inner, stable shells can, for our purpose, be ignored. The L shell of neon may have two types of electron orbitals. These are the s orbital ($l = 0$) and three p orbitals ($l = 1$; $m = -1, 0$, and $+1$). Each orbital can hold one *pair* of electrons (opposite in spin).

To form a neon-like molecule, a $2p$ orbital of the fluorine atom and the $1s$ orbital of the hydrogen atom might be considered to form one bonding molecular orbital, while the s orbital and two of the p orbitals of the fluorine atom remain unchanged. We thus arrive at a neon-like hydrogen fluoride molecule (Fig. 4-5). What actually occurs may be somewhat more complex than this, but the details are more readily understood after the carbon system has been considered.

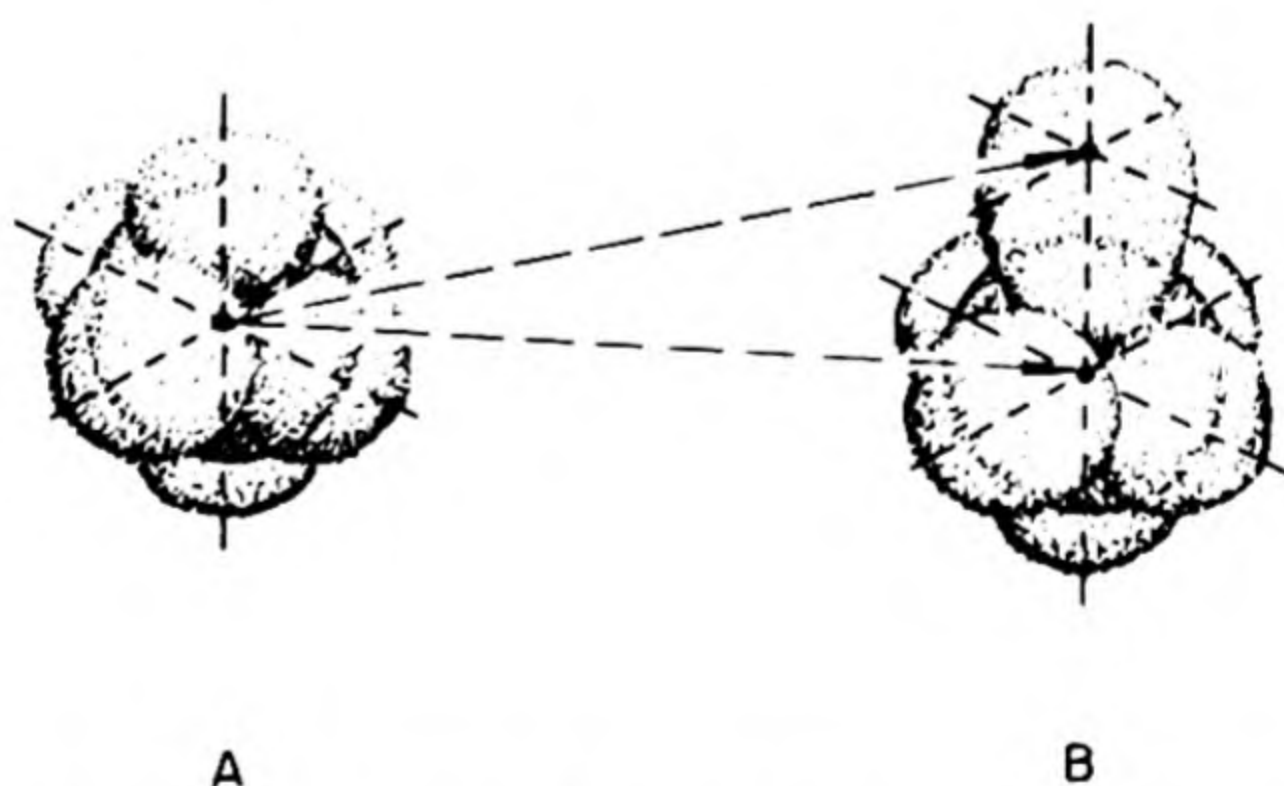


Fig. 4-5. Preliminary Approximation of Formation of a Neon-like Molecule by Combination of Hydrogen and Fluorine. (A) Neon $2s$ and $2p^3$ -orbitals, (B) $\text{H}-\text{F}$ σ molecular orbital and $2p_y$, $2p_z$, and $2s$ atomic orbitals.

F. Atomic Orbitals

The locus of an electron in a given energy level of an atom is called an *atomic orbital* (AO). The distribution of the electron can be surmised from the wave nature of the electron. The wave equation for a *K* shell electron, such as that of the hydrogen atom (Figs. 4-6 and 4-7), reveals that the electron can be found anywhere in space, but is most probably found near the atomic nucleus (99% within about one Å). The atomic orbital occupied by electrons in the ground state of the hydrogen atom or helium atom (Fig. 4-8A) is called an *s* orbital and is spherically symmetrical.

The *2s* orbital is similar to the *1s* orbital; it is spherically symmetrical. However, the three *2p* atomic orbitals are twin-lobed orbitals, *one* of

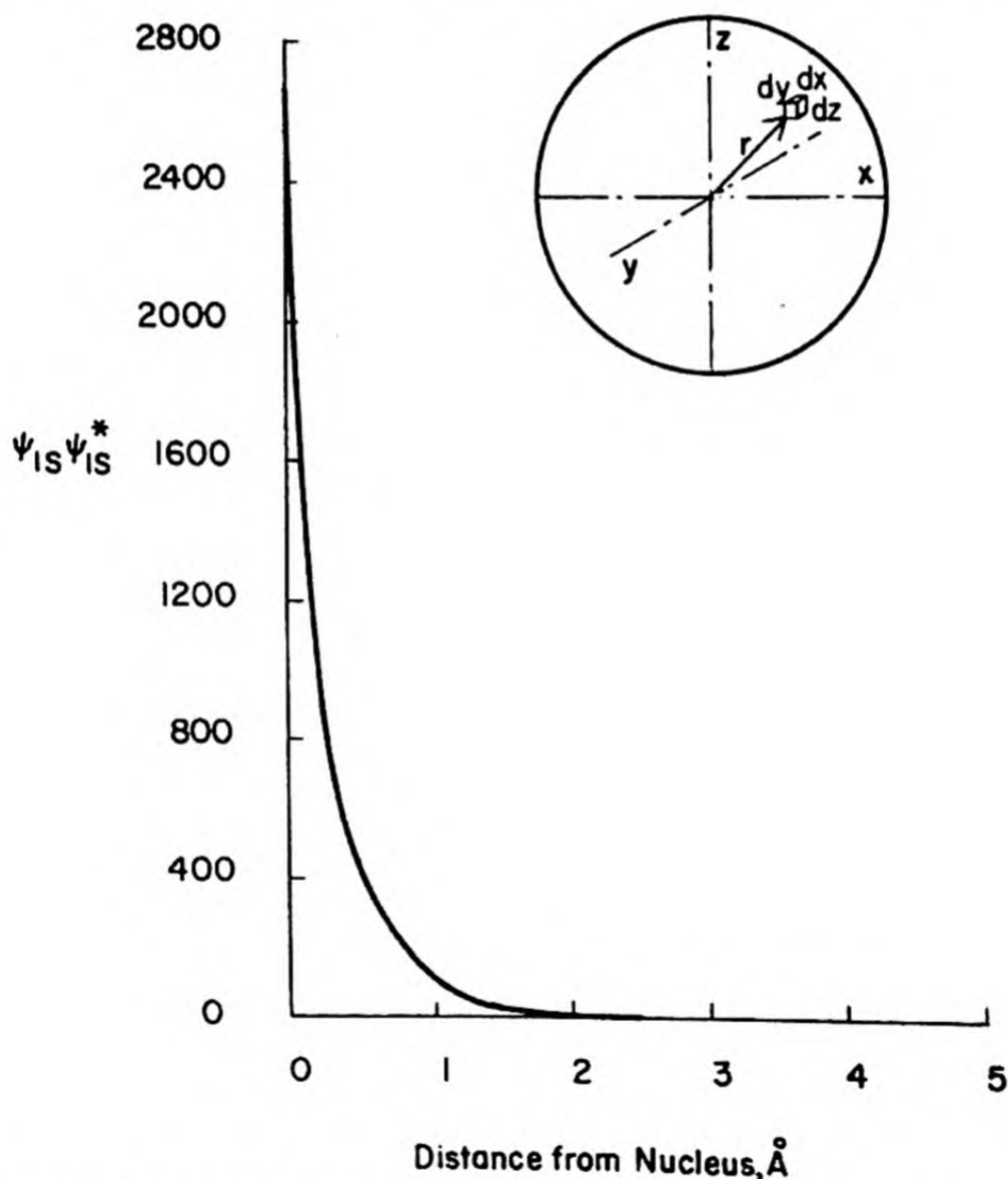


Fig. 4-6. Probability Density Distribution of Hydrogen *s* Orbital Electron (probability of finding electron in volume element $dx dy dz$ at distance r from nucleus). ψ is the wave function for the *1s* orbital.

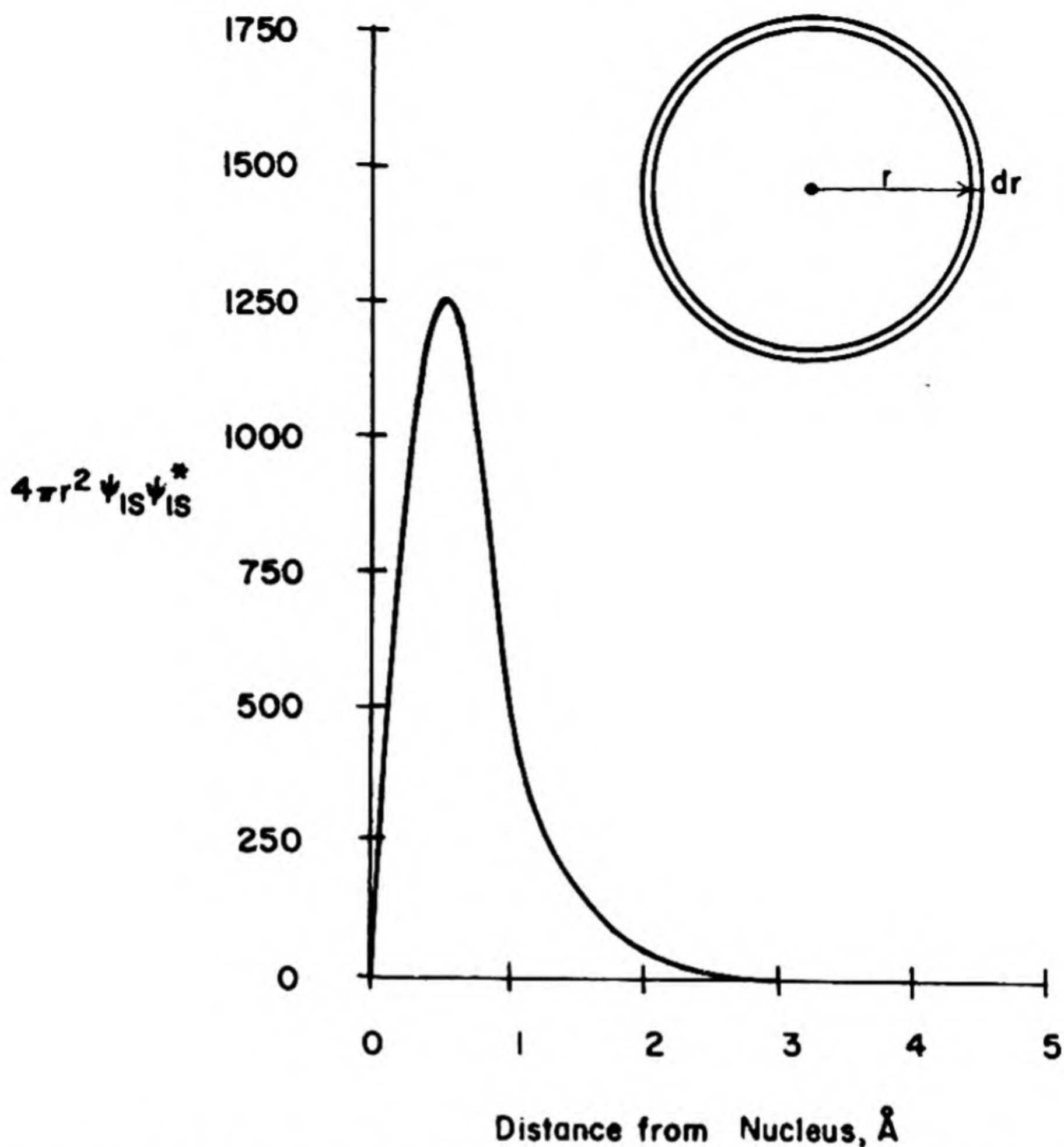


Fig. 4-7. Radial Probability Distribution of Hydrogen s Orbital Electron (probability of finding electron in spherical shell of thickness dr at distance r from nucleus).

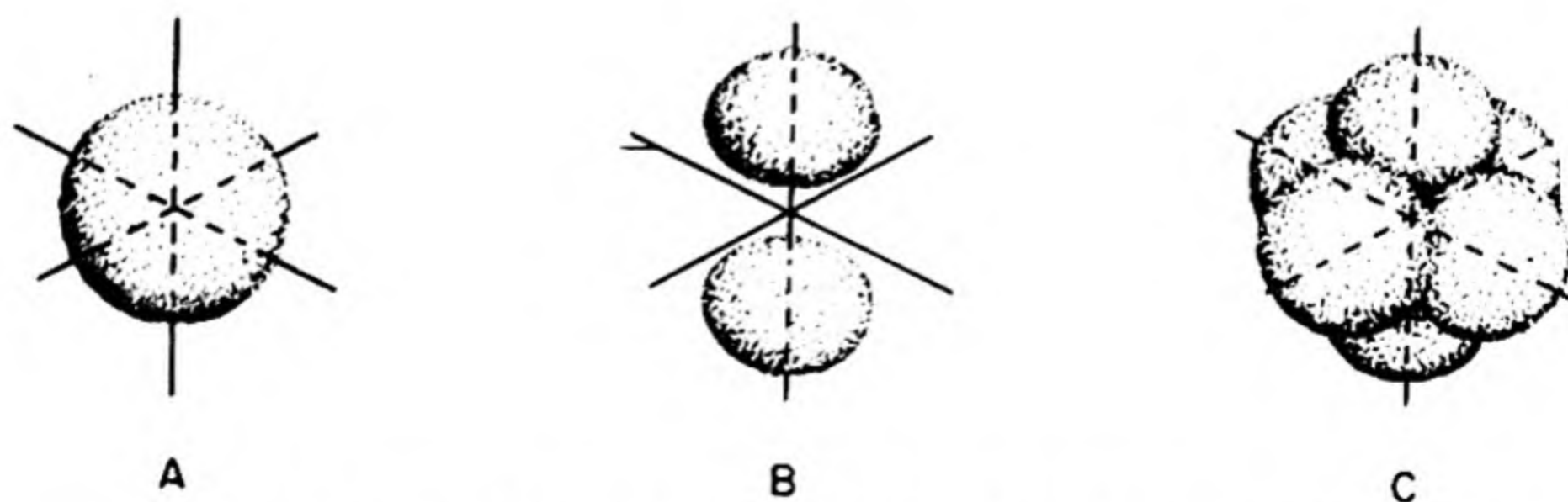


Fig. 4-8. Atomic Orbitals. (A) s orbital, (B) p orbital, (C) p^3 orbitals.

which is shown in Fig. 4-8B, each at right angles to the other two (Fig. 4-8C). The two lobes of a p orbital belong to the *same* orbital.

Since the p orbitals are directed toward the three Cartesian axes, x , y , and z , they are designated p_x (with its axis of rotation in the x axis), p_y , and, p_z . The details of atomic orbital structure depend on reasonable, but approximate, quantum mechanical assumptions; only indirect experimental evidence, if any, is available to support them.

The five d orbitals ($l = 2$) and seven f orbitals ($l = 3$) in a given shell are somewhat more complex. Since they play less important roles in organic compounds than s orbitals and p orbitals, they are not described here.

G. Molecular Orbitals

The fact that electrons from different atoms interact to form a covalent bond between atoms indicates that something occurs between the atomic orbitals. The interaction is described in different ways, depending on the point of view, each a different aspect of the covalent bond. Electron spin coupling is involved; this means that the two separate AO's combine to form a single bonding molecular orbital (MO), in which only two electrons with opposite spins can exist. The new system also contains an antibonding MO, but this higher-energy MO is empty in the ground state of the molecule. The aufbau principle applies to molecular orbitals as well as atomic orbitals (§4-1A).

Like an AO, an MO is the probability density distribution of electrons in a specific energy state. An MO differs from an AO, however, in that the former includes at least two atomic nuclei, the latter only one.

A molecular orbital may be considered to be formed by an overlapping interaction of two or more atomic orbitals. This is illustrated for the hydrogen molecule in Fig. 4-9. Although the degree to which atomic orbitals overlap in the formation of a molecular orbital is one criterion of the stability (dissociation energy) of a bond, more occurs than mere overlapping, since both the shape and electron distribution in the molecular

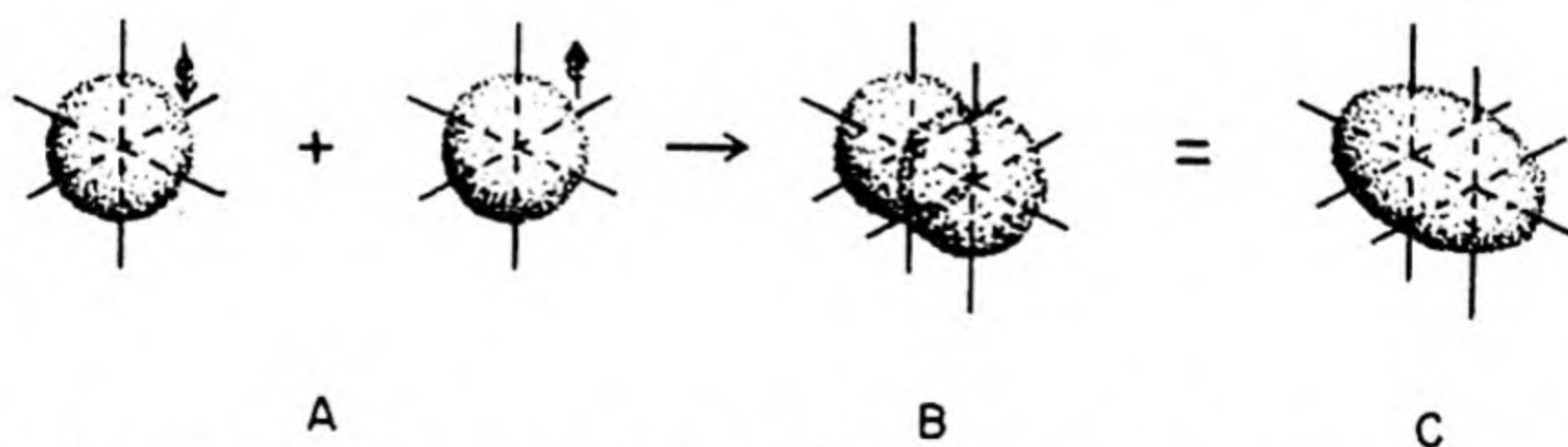


Fig. 4-9. Combination of Atomic Orbitals of Two Hydrogen Atoms to Form a Molecular Orbital. (A) Separate atomic orbitals, (B) Overlapping representation of molecular orbitals, (C) More accurate elliptical orbital formed by coalescence of atomic orbitals.

orbital are considered to differ from a simple summation of atomic orbitals.

The analogy between the hydrogen molecular orbital and the $1s$ atomic orbital led to designation of the hydrogen MO as a σ orbital. This MO, formed from two $1s$ AO's, is one of several closely related types called σ (sigma). A σ MO is characteristic of a single bond and also occurs as the lowest-energy orbital of each multiple bond.

(1) *Molecular Energy Levels.* When two or more AO's combine, the same number of MO's result. In the simple case of the hydrogen molecule, the AO's interact to produce one MO of greater stability (lower energy content) than the original AO's, called a *bonding orbital*, and one MO of lesser stability (high energy content), called an *antibonding orbital* (see Fig. 4-10).

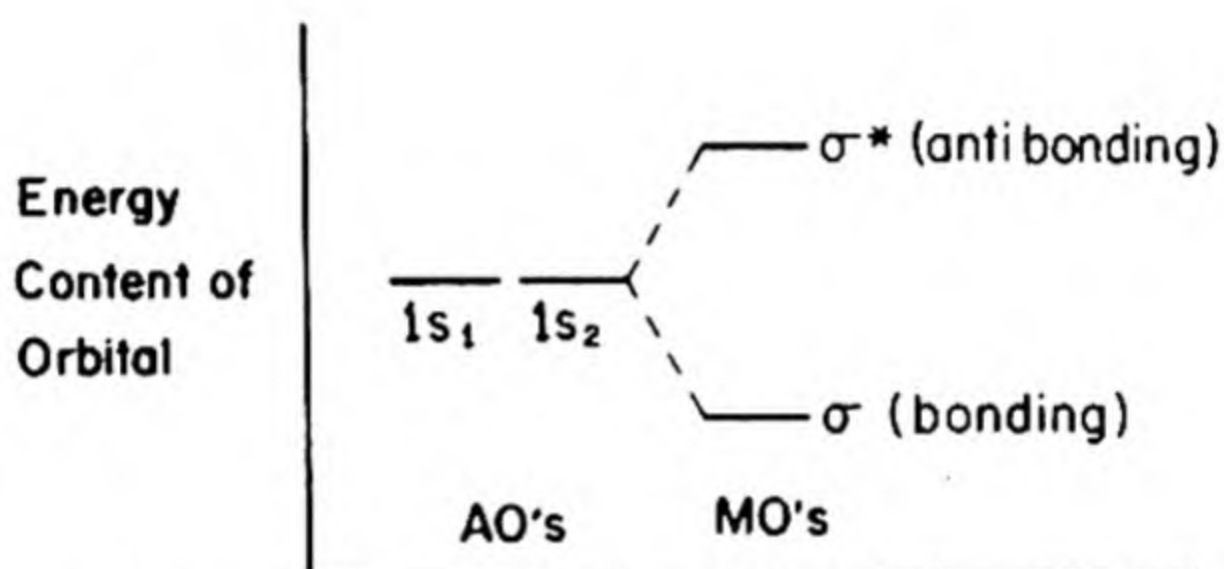
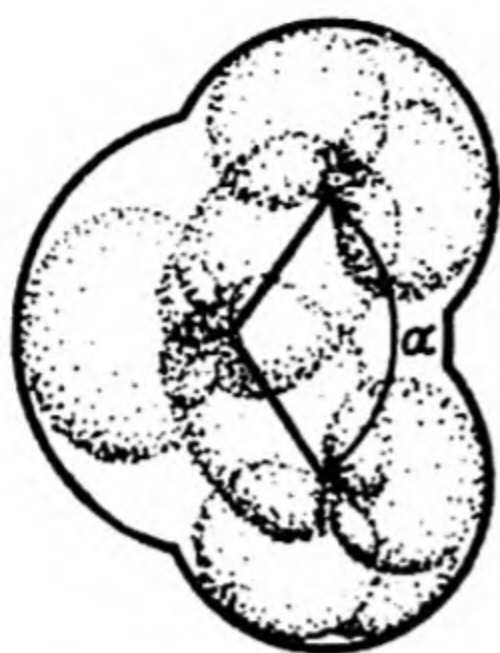


Fig. 4-10. Energy Diagram for Molecular Orbital Formation in Hydrogen.

Since each orbital can hold up to two electrons (differing in spin quantum number), the two electrons of the hydrogen molecule reside in the bonding orbital in the ground (unexcited) state. A third electron would have to go into a higher-energy orbital to give a less stable species.

The summation for all the electrons in the orbital of the energy difference between the MO and the AO's is called *resonance energy*. The resonance energy plus the energy due to coulombic forces (electrical charges) is the bond dissociation energy (§4-1D).

(2) *Orbital Hybridization.* The simple MO approach used in §4-1C and §4-1E can be tested more fully in the cases of polyatomic molecules, HOH, NH_3 , and CH_4 , than in the cases of simple diatomic molecules thus far described. One would predict in these cases that at least some of the H—X—H bond angles (see Fig. 4-11) would be 90° , since the H—X sigma bonds formed between the p orbitals of X and s orbital of H would be restricted by the geometry of the p atomic orbitals (§4-1F) to 90° angles about X. Since the $2s$ orbital of X is nondirected, a fourth sigma orbital

Fig. 4-11. Bond angle, α .

between the $1s$ of H and $2s$ of $X = C$ might assume any position relative to the others, say as far away as possible, so as to form an *irregular* tetrahedron.

In fact, however, experimental measurements of such angles by dipole moments (Chapter 35) and electron diffraction (Chapter 36) show $H-X-H$ angles significantly larger than 90° . Furthermore, the CH_4 molecule is *perfectly symmetrical*. All four hydrogen atoms are identical and equally restrained in their positions as if all four bonds were identical. Such can be the case only if the characters of the s orbital and three p orbitals of the carbon atom have become completely mixed so that each bonding orbital has $\frac{1}{4}$ s and $\frac{3}{4}$ p character at carbon. This is called *bond hybridization*.

A useful approach is to consider a molecular system as a *linear combination of atomic orbitals* (LCAO) (§4-1G). According to this viewpoint, linear overlapping of either s orbitals or p orbitals is poorer, hence less stable, than linear overlapping of orbitals somewhere between s and p in character (Fig. 4-12). Hence, intermediate or *hybrid* orbitals form more stable bonds than pure s or pure p orbitals.

Figure 4-13 shows the relative energies of the atomic orbitals in a second period element. The lowest-energy orbital ($1s$) is the closed, stable shell not used in chemical bonding, while the $2s$ and $2p$ orbitals are avail-

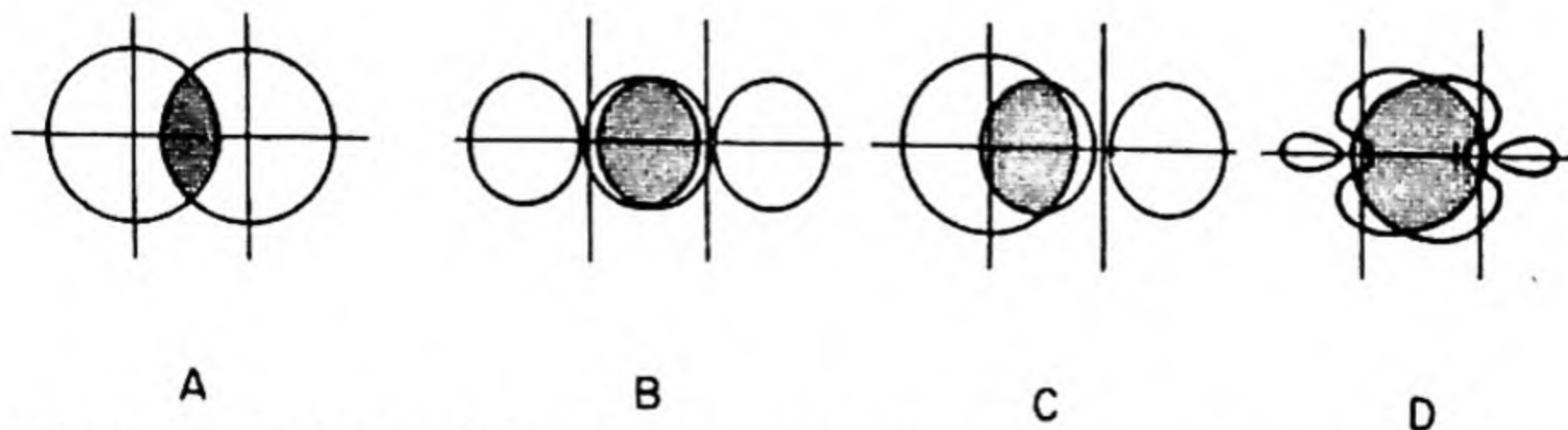
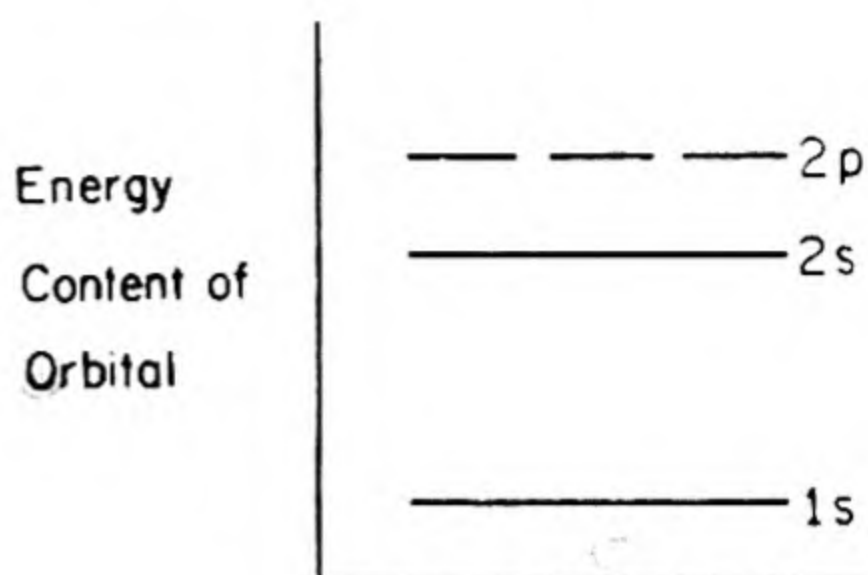


Fig. 4-12. Degree of Overlapping in Various Types of Orbital Systems. (A) s Orbitals, (B) p Orbitals, (C) s Orbital and p Orbital, (D) Intermediate (hybrid) orbitals.

Fig. 4-13. Relative Energy Contents of Simple Atomic Orbitals.



able for valence electrons. Hybrid orbitals lie between $2s$ and $2p$ in energies, proportional to the amount of s and p character they contain.

In CH_4 the gain in stabilization energy by better overlap is made at no expense, since all four orbitals are utilized in bonding and the total of energies of the four sp^3 hybrid AO's (one s and three p orbitals \rightarrow four sp^3 hybrids) is the same as the total of energies of unhybridized AO's of the parent system. However, better bonding can be attained in hybrid MO's than unhybridized MO's. Thus, there is a very strong tendency for a carbon atom attached to four other groups to hybridize its orbitals. This results in a normal bond angle of 109.5° for *tetrahedral* carbon.

Similarly, water and ammonia obtain best stability through hybrid MO's. However, the s and p character are not necessarily equally distributed among the bonds and the unshared electron pairs. This may explain deviations of bond angles in these compounds (105° in water, 108° in ammonia) from regular tetrahedral angles.

It is apparent from the discussion above that the amount of s and p character in hybrid bonding orbitals is reflected in molecular geometry. Four ideal systems are recognized (Fig. 4-14). One has already been mentioned, the sp^3 tetrahedral system shown in Fig. 4-14C. The other hybridized systems are the sp^2 system, which is trigonal (bond angles 120°) (Fig. 4-14B), and the sp system, which is *digonal* or linear (bond angle 180°) (Fig. 4-14A). The fourth, unhybridized, system, may occur in bonding of some elements in higher periods, such as sulfur.

It is seen that more p character decreases bond angles ($180^\circ \rightarrow 120^\circ \rightarrow 109.5^\circ \rightarrow 90^\circ$). The ideal systems characterize certain types of bonds with the angles of the actual bonds distributed more or less about the ideal angles, depending on molecular forces not thus far considered.

A sigma molecular orbital is formed by the *longitudinal* overlapping of any combination of s , p or sp^n hybrid AO's. The sp^3-sp^3 σ orbital of ethane is illustrated in Fig. 4-15A.

(3) *Multiple Bonds*. In the most common molecular orbital treatment, a double bond is considered to have two kinds of molecular orbitals. The first of these is a σ orbital formed from two sp^2 AO's which overlap with

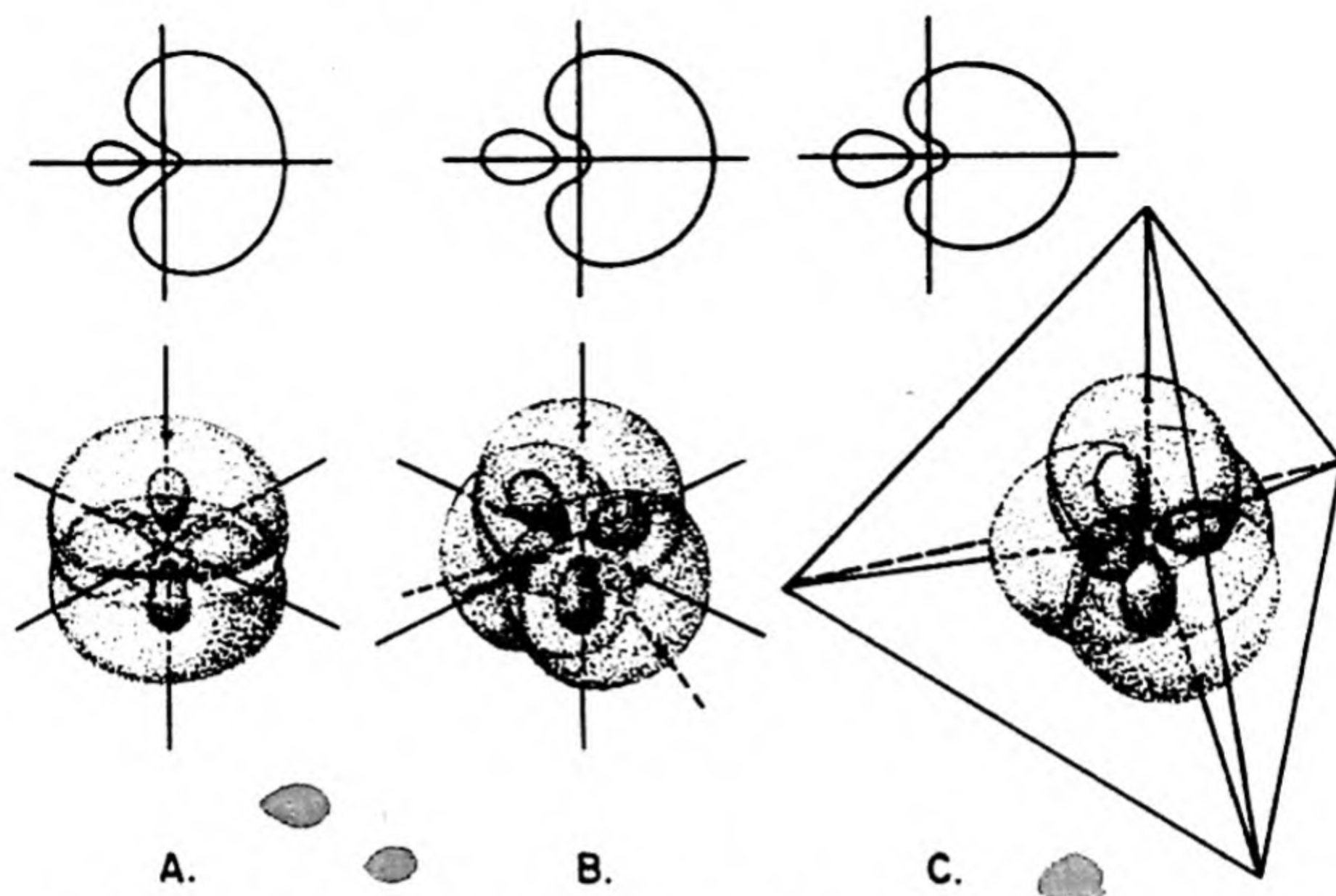


Fig. 4-14. Hybridized Atomic Orbitals. (A) sp hybrid orbitals (at 180°), (B) sp^2 hybrid orbitals (at 120°), (C) sp^3 hybrid orbitals (tetrahedral).

their axes in the direction of the bond. Consideration of a trigonal carbon atom with three sp^2 AO's and one p AO indicates that the axis of the p orbital is at right angles to the plane of the three sp^2 's. When two such atoms are combined (Fig. 4-16A), the two p orbitals can overlap only in a parallel fashion (Fig. 4-16B); the molecular orbital thus formed (Fig. 4-16C) is termed a pi (π) MO. The σ and π orbitals in ethylene are shown

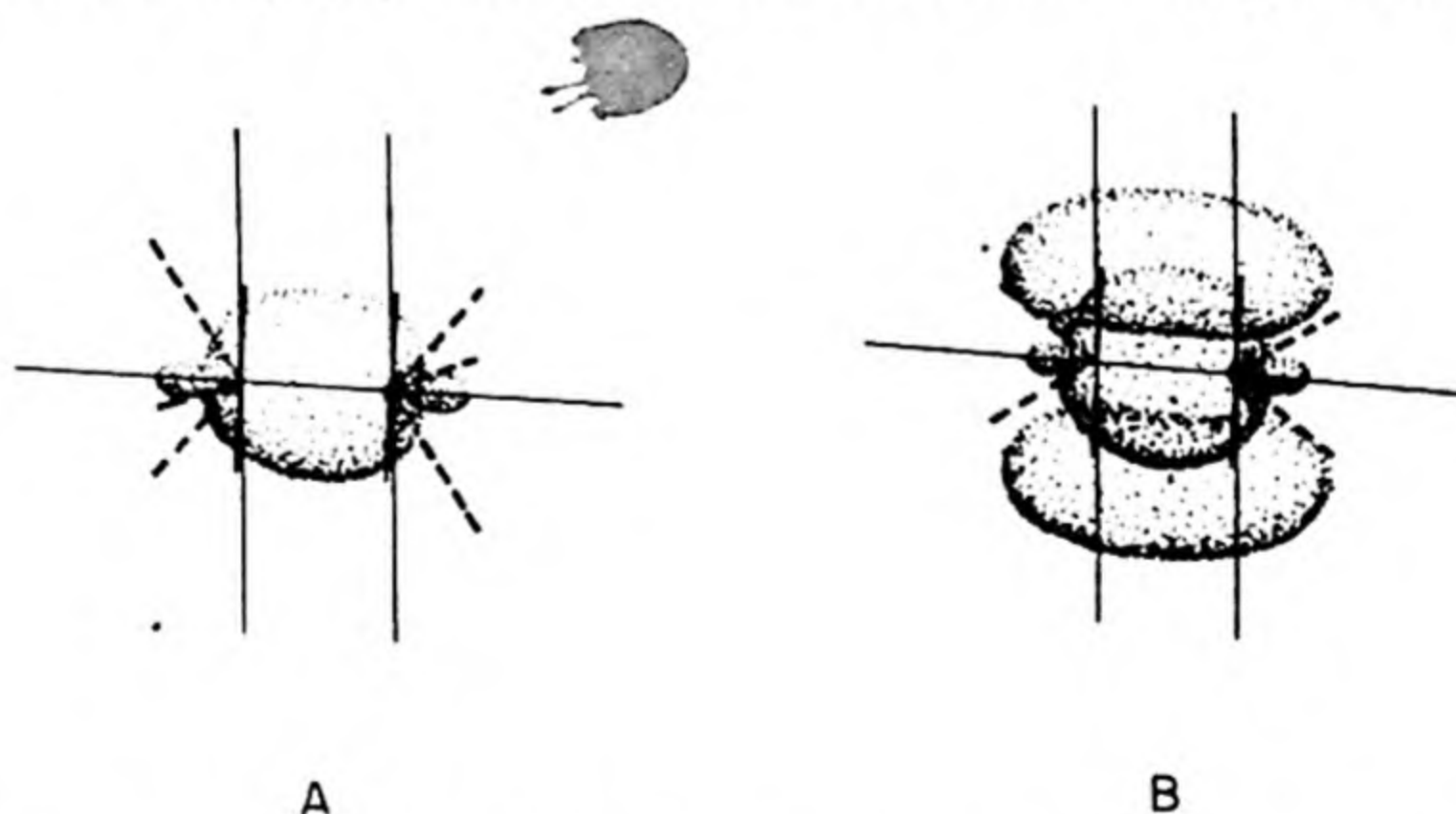


Fig. 4-15. Hybridized Molecular Orbitals. (A) One of the several sp^3 hybrid σ orbitals of two carbon atoms; directions of others shown by dash lines, (B) sp^2 hybrid σ orbital and π orbital connecting carbon atoms by double bond; directions of other σ orbitals shown by dash lines.

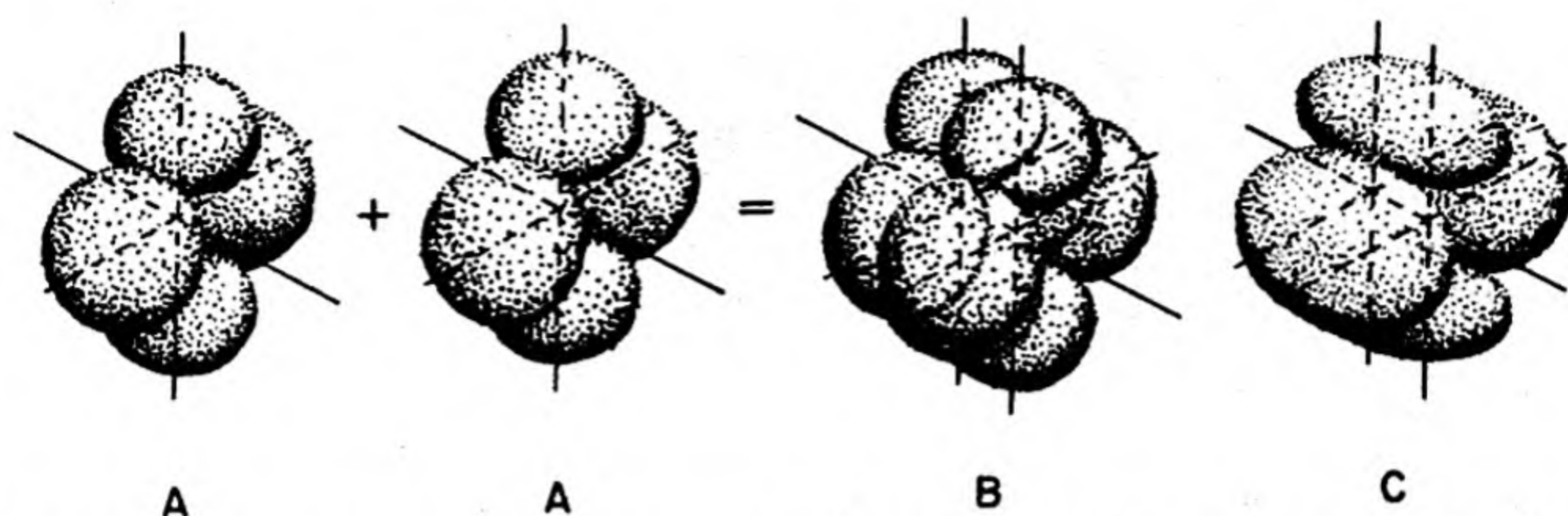
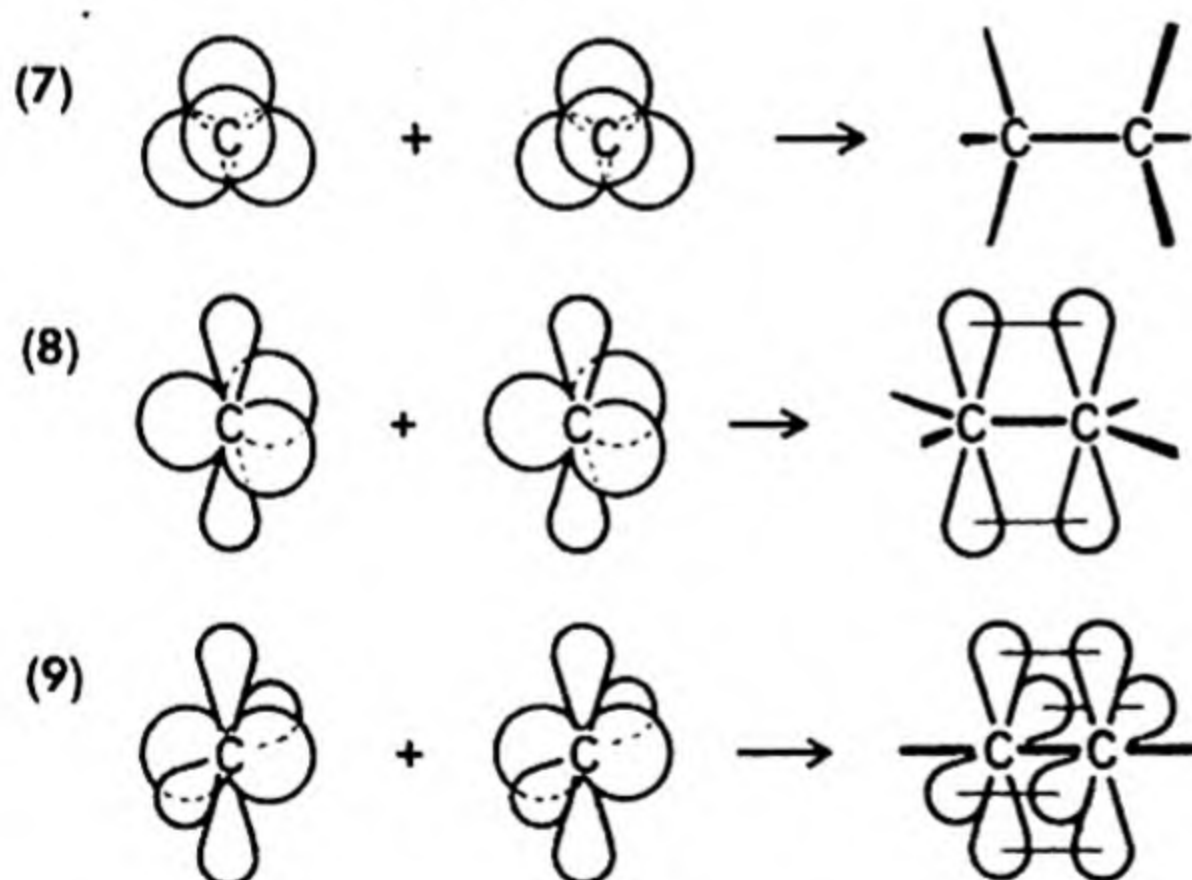


Fig. 4-18. Combination of Two Atomic p^2 Orbitals to Form Two π Molecular Orbitals. (A) Atomic orbitals, (B) Overlapping model of π^2 MO, (C) Coalescing model of π^2 MO.

H. Orbital Formulation

It is inconvenient to attempt to represent AO's and MO's by their probability density clouds, hence these features have been conventionalized. Sigma orbitals are represented by straight lines (or occasionally ellipses) joining the elementary symbols. Pi orbitals are represented by p loops joined by tie lines. Formation of the σ , $\sigma\pi$, and $\sigma\pi^2$ bonds of ethane, ethylene, and acetylene (C_2H_2) are notated according to Eqs. (7) through (9).



4-2. MOLECULAR PROPERTIES

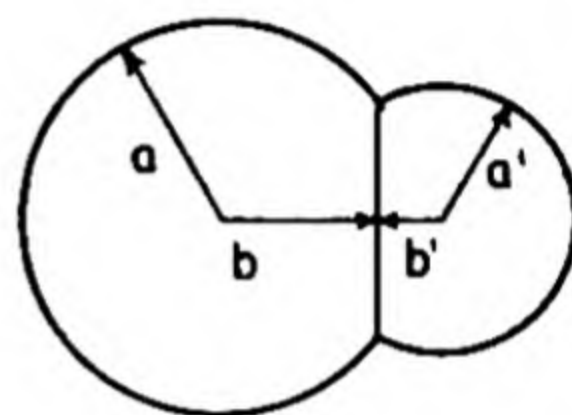
A. Geometry

Atoms covalently bound together are most stable when their nuclei are at some definite distance apart (§4-1D and Fig. 4-4B). The study of a large number of compounds indicates that each atom in a particular type of bond contributes a nearly constant, characteristic increment to the bond distance. For example, the C—C bond distance in ethane, 1.542 Å, and

the H—H bond distance in hydrogen, 0.74 Å, average to give nearly the C—H bond distance in ethane, 1.094 Å. The increment contributed by each atom, 0.77 Å for carbon and 0.37 Å for hydrogen, is its covalent bond radius. This varies significantly with the type of bond (single, double, triple).

Parts of unattached atoms or different molecules contiguous to each other show radii different from covalent radii. As illustrated in Fig. 4-4A, nonoverlapping atomic and molecular orbitals repel each other out to some definite distance. These *nonbonding interactions* give rise to (somewhat elastic) nonbonding radii. The distinction between covalent and nonbonding radii is shown in Fig. 4-19.

Fig. 4-19. Atomic Dimensions. a, a' = Atomic non-bonding radii. b, b' = Covalent radii. $b + b'$ = bond distance.



The effects of varying kinds of orbital hybridization on bond angles have been discussed (§4-1G(2) and §4-1G(3)). Bond distances are also sensitive to kinds of orbital hybridization, as well as to the multiplicity of the bonds.

Those orbitals with more s character (Fig. 4-14) are shorter and result in shorter bonds than those with less s character. Variation of single bond radii of carbon atoms with orbital hybridization, $sp^3 > sp^2 > sp$, is shown

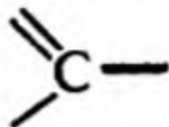
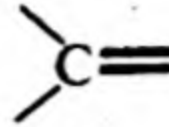
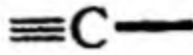


in Table 4-2. Thus, the system $\begin{array}{c} \text{sp}^2 \quad \text{sp}^3 \\ \diagup \quad \diagdown \\ \text{C} = \text{C} - \\ \diagdown \quad \diagup \end{array}$ has a shorter bond length (1.50 Å) than the system $\begin{array}{c} \text{sp}^3 \quad \text{sp}^3 \\ \diagup \quad \diagdown \\ \text{C} - \text{C} - \\ \diagdown \quad \diagup \end{array}$ (1.54 Å).

Addition of one or more π orbitals to a bond introduces additional attractive forces between the bound atoms, hence shortens the bond distances (Table 4-3).

TABLE 4-2. Single Bond Radii vs. Hybridization

Orbital	Bond	Radius, Å
sp^3	$\begin{array}{c} \diagup \\ \text{C} - \\ \diagdown \end{array}$	0.77
sp^2	$\begin{array}{c} \diagup \\ \text{C} = \\ \diagdown \end{array}$	0.73
sp	$\begin{array}{c} \text{C} \equiv \\ \text{C} - \end{array}$	0.69

TABLE 4-3. Bond Radii vs. Bond Multiplicity and Bond Hybridization

Orbitals	Bond	Radius, Å
$sp^2(\sigma)$		0.73
$sp^2(\sigma) + p(\pi)$		0.67
$sp(\sigma)$		0.69
$sp(\sigma) + p(\pi)$		0.64
$sp(\sigma) + p^2(\pi^2)$		0.60

B. Rotations in Molecules

Molecules are far more mobile and more flexible than paper formulas or ball-and-peg models would seem to indicate. Molecular motions take a variety of forms, of which the fundamental types are illustrated in Fig. 4-20.

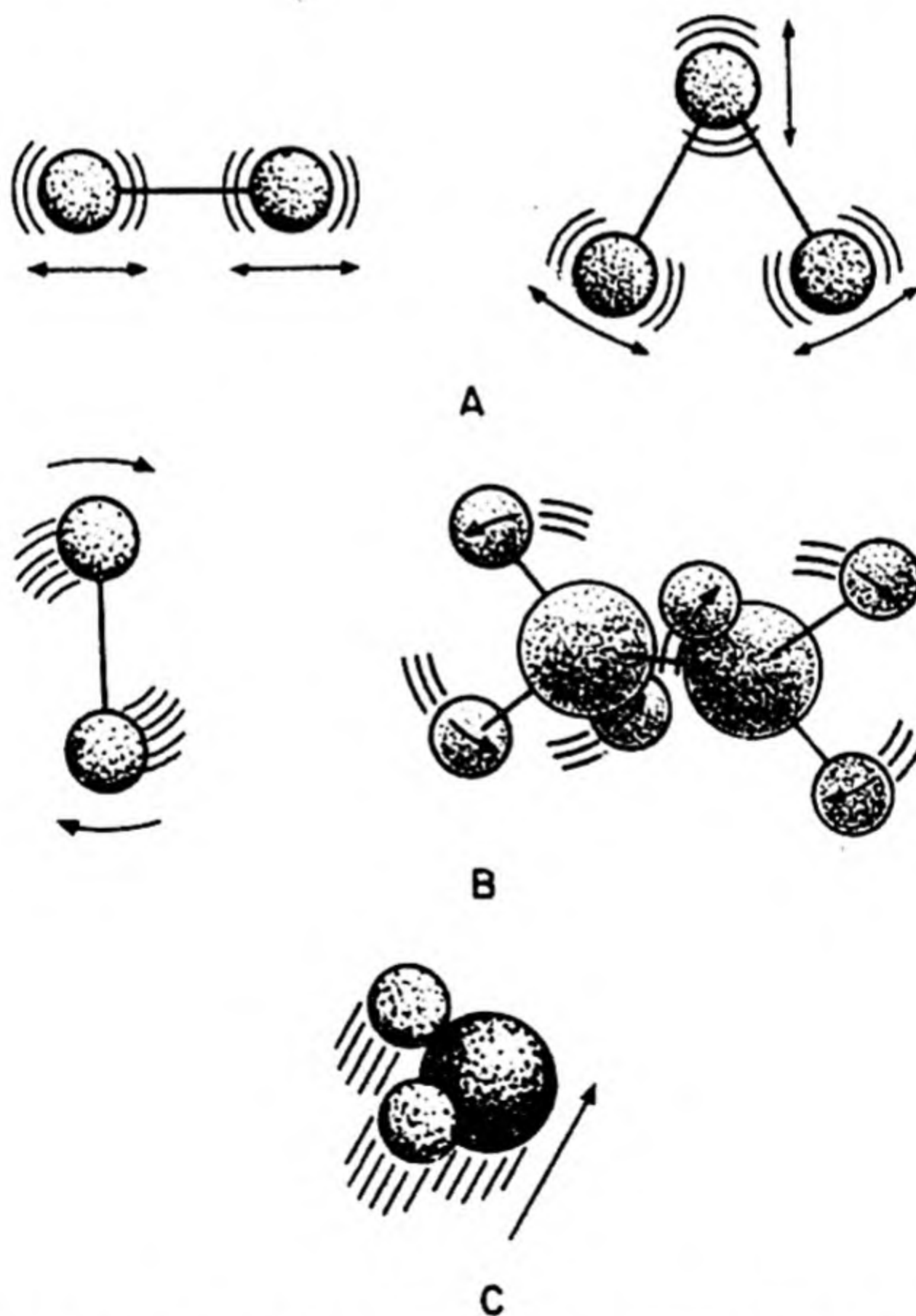


Fig. 4-20. Types of Molecular Motion. (A) Vibrations, (B) Rotations, (C) Translation.

Single (σ orbital) bonds (Fig. 4-15A) are cylindrically symmetrical, hence allow almost complete freedom of rotation of the other MO's about them (Fig. 4-21A). However, the other groups (the H-atoms in Fig. 4-21A) cannot pass by each other, since to do so would require distortions of bond angles in the sp^3 system too far from the hybridization angle. Thus, those groups on the same atom must maintain the same positions relative to each other, but can rotate past the groups on the adjacent carbon atom.

On the other hand, p orbital pairing completely blocks rotation of the groups about the $\sigma\pi$ double bond at room temperature (Fig. 4-21B).

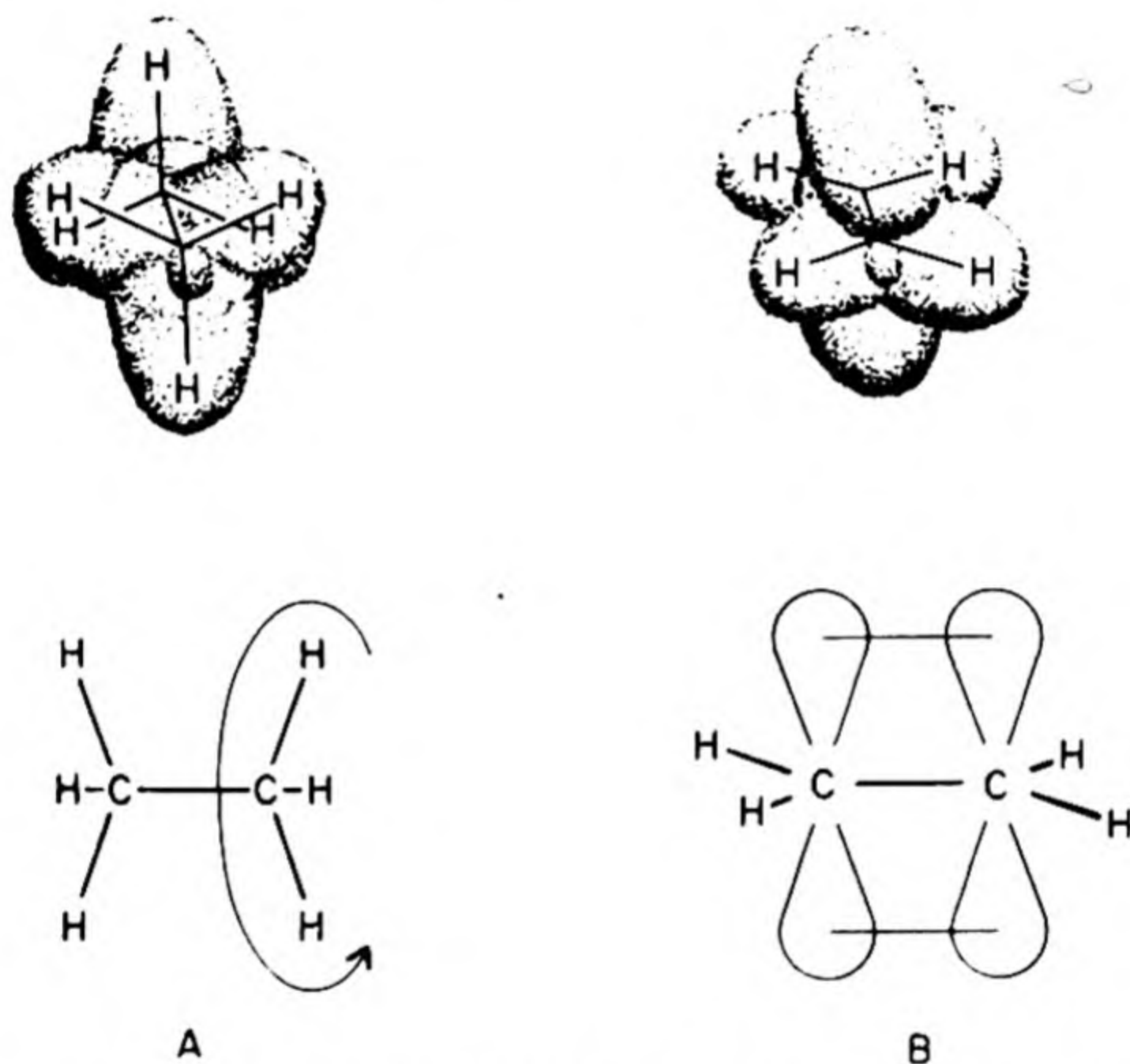
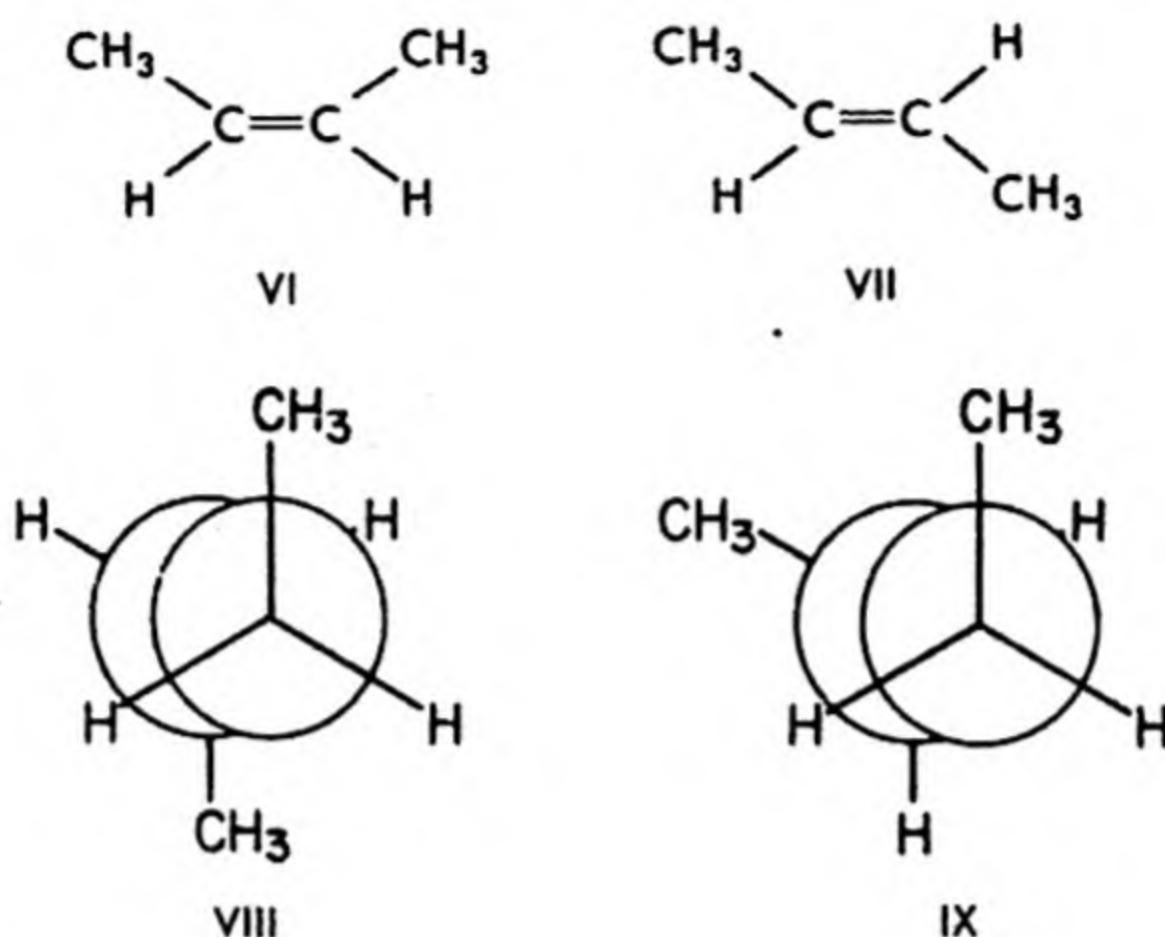


Fig. 4-21. Complete MO Diagrams and MO Formulas for Ethane and Ethylene. (A) Ethane, rotation permitted, (B) Ethylene, showing π MO tie which prevents rotation.

Again, the p orbitals and σ orbitals on a single carbon atom must maintain their relative geometries. Thus, tying of the p orbitals into a pi orbital (Figs. 4-15B and 4-21B) fixes the relative geometries about both of the connected atoms. To cause groups to rotate about a $\sigma\pi$ bond requires uncoupling of the π orbital (equivalent to transferring electrons from the π MO to the p AO's), a high-energy process (Fig. 4-17), or destruction of the π orbital momentarily by a chemical reaction.

Consequently, the two butenes, VI and VII, are separately isolable isomeric compounds. They are called geometric isomers since they differ

in the spatial orientation or configuration of their groups. On the other hand, the different conformations, VIII and IX, of *n*-butane readily rotate from one to the other and are not separately isolable.

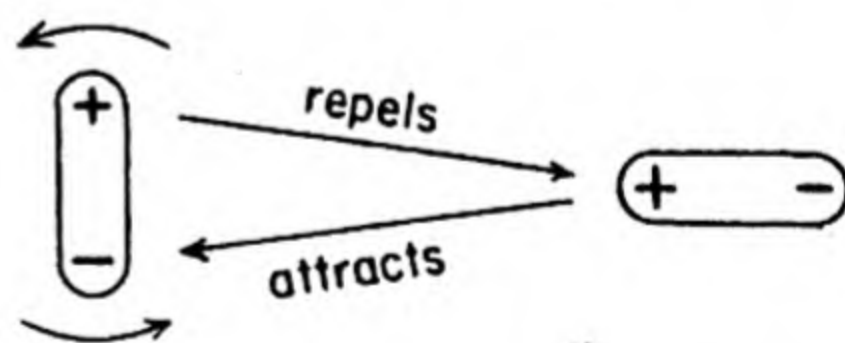


C. Molecular Polarity

The unequal distribution of electrons in the orbitals between atoms that differ in electronegativity may result in making one portion of the molecule permanently more negative, another more positive. (Only when the electronegativity differences are directed so as to cancel each other, as in methane, carbon tetrachloride, and other similar molecules, does the covalent compound have nonpolar molecules.)

Polar molecules tend to become oriented with respect to electrical fields, including those of other polar molecules (Fig. 4-22). Such orientation

Fig. 4-22. Forces Exerted on One Polar Molecule by Another.

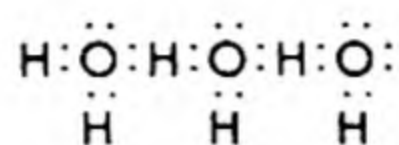


results in maximizing attractive forces and minimizing repulsive forces between the molecules. Where polar forces are large, they have significant effects on physical properties. Large intermolecular polar attractions tend to raise boiling points and melting points and to increase densities.

D. Hydrogen Bonding

A hydrogen bond (also called hydrogen bridge) is an attraction between two molecular units through a hydrogen atom attached to one unit and an

unshared pair of electrons attached to the other unit, as in water. The



hydrogen bonded
(associated) water

stability of the connection varies from chemical association, as in the bifluoride ion ($:\ddot{\text{F}}:\text{H}:\ddot{\text{F}}:$)⁻, to weak physical association little stronger than other attractions between polar molecules.

Hydrogen bonding occurs in compounds in which the hydrogen atoms are *positive* ends of polar molecules. These electron-hungry hydrogen atoms attract unshared electrons on atoms which are *negative* ends of polar molecules. Hydrogen bonding strong enough to cause obvious abnormalities in properties is generally limited to cases in which the hydrogen atoms are bound to nitrogen, oxygen, or fluorine and in which the unshared electron pair is also on one of these elements. These are elements with which hydrogen forms unusually strong covalent linkages, as is indicated by the exceptionally low acid strengths of the acids NH_3 , H_2O , and HF . Weaker hydrogen bonds have been detected in a variety of other cases, some of which are considered at the appropriate places.

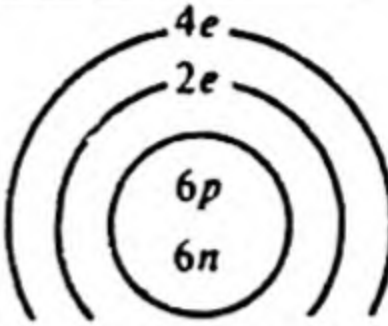
Hydrogen bonding, by greatly increasing the effective size of unit particles (or by greatly increasing attractive forces between molecules), results in higher melting points and boiling points than is expected for molecules of a given molecular weight. The effect is similar to that of other polar attractions, but is often much greater. Thus, water, molecular weight 18, boils 124° higher than methyl ether, CH_3OCH_3 , molecular weight 46. Both contain polar molecules, but only water exhibits strong hydrogen bonding.

4-3. CARBON AND ITS PROPERTIES

Carbon appears in the middle of the second period of the periodic table. The structures of the carbon atom and its kernel are summarized in Table 4-4.

In keeping with its central position in the period, carbon is stable only when it shares electrons. The ultimate example of such sharing is in the elementary forms of carbon, diamond and graphite. Diamond consists of carbon atoms covalently bound to each other by single bonds only. The hardness and relative inertness of diamond are testimony to the strength and stability of the carbon-to-carbon bond. The arrangement of the atoms in a diamond crystal, as interpreted from X-ray scattering photographs, is illustrated in Fig. 4-23.

TABLE 4-4. Atomic Structure of Carbon

Symbol	C
Atomic Number	6
Atomic Structure	
Energy Levels	$1s^2$ $2s^2 2p^2$
Kernel Structure	$\left[\frac{6p, 6n}{1s^2} \right]^{+4}$
Electronic Diagram of Atom	$\cdot \underset{\cdot}{\underset{\cdot}{\text{C}}} :$

In graphite (Gk. *graphein*, to write), the carbon atoms are also covalently bound, but only within layers, whereas the bonding in diamond is three dimensional throughout the crystal. Fig. 4-24 illustrates the arrangement of atoms in graphite as interpreted from X-ray studies. Since there are no chemical bonds between layers, these can easily slip over each other, particularly when air molecules wedge the layers apart and cause them to roll up and act as bearings. Conductivity is due to transfer of electrons through the layers by a process of electron leap-frog through the pi orbitals of the alternating double and single bonds (Fig. 4-25). (Again, a crude model is presented; the double and single bonds are not localized as this diagram would imply.)

Carbon is a mild reducing agent. It reacts directly with oxygen, sulfur, and halogens, but only at high temperatures. Its affinity for oxygen is

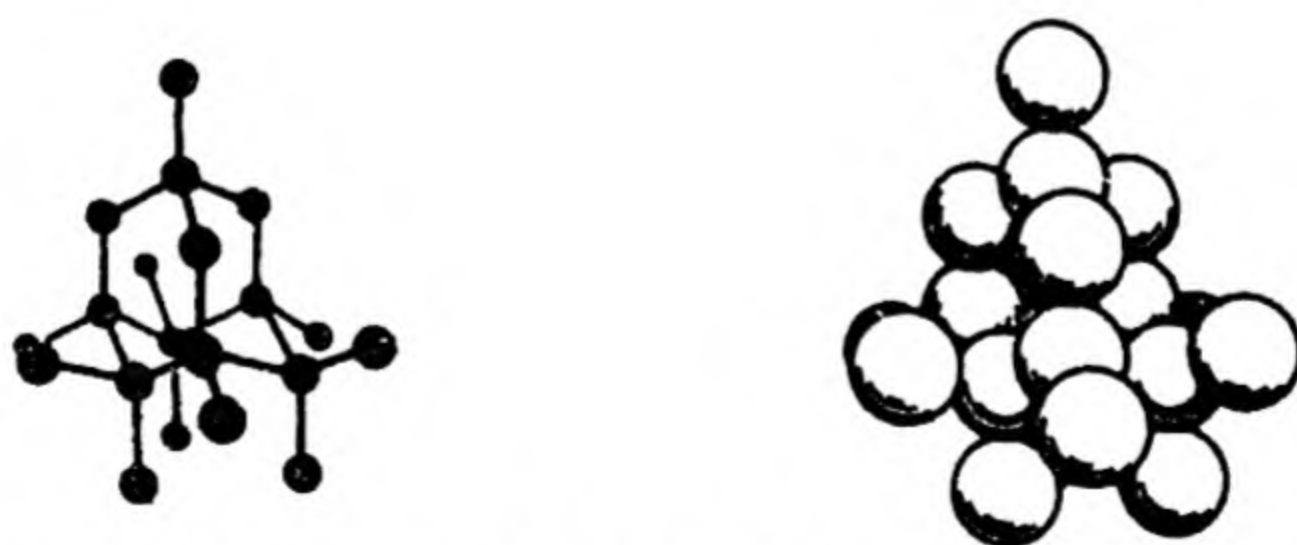


Fig. 4-23. Diamond Crystal Lattice. Typical tetrahedral sigma orbital hybridization for carbon atoms with all single bonds.

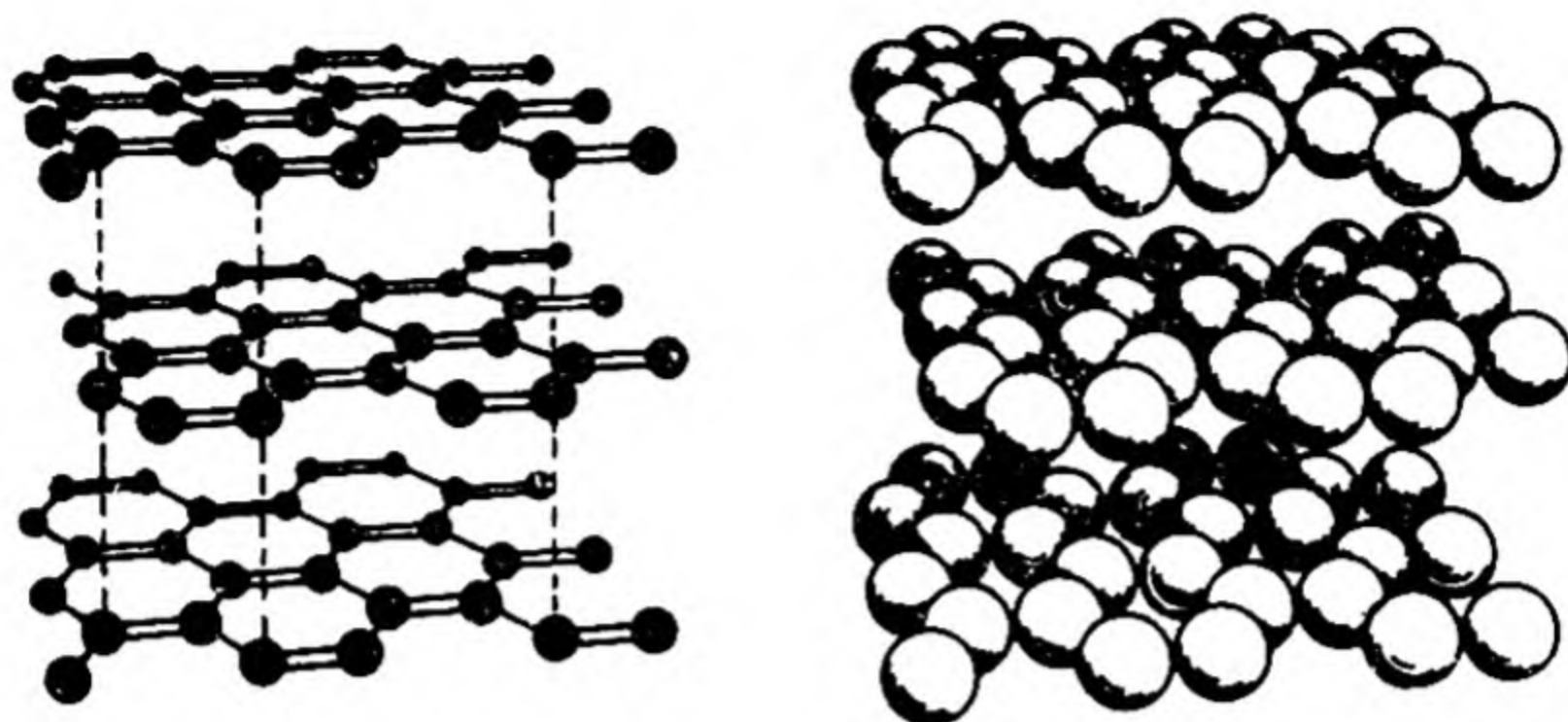


Fig. 4-24. Graphite Crystal Lattice. Typical trigonal (planar 120°) sigma orbital hybridization for carbon atoms with two single and one double bonds.

sufficient to remove this element from several metal oxides and water, again at high temperatures.

Carbon shows remarkable ability to form covalent bonds with atoms of other elements as well as with other carbon atoms. Multiple bond formation with atoms of other Period 2 elements as well as with other

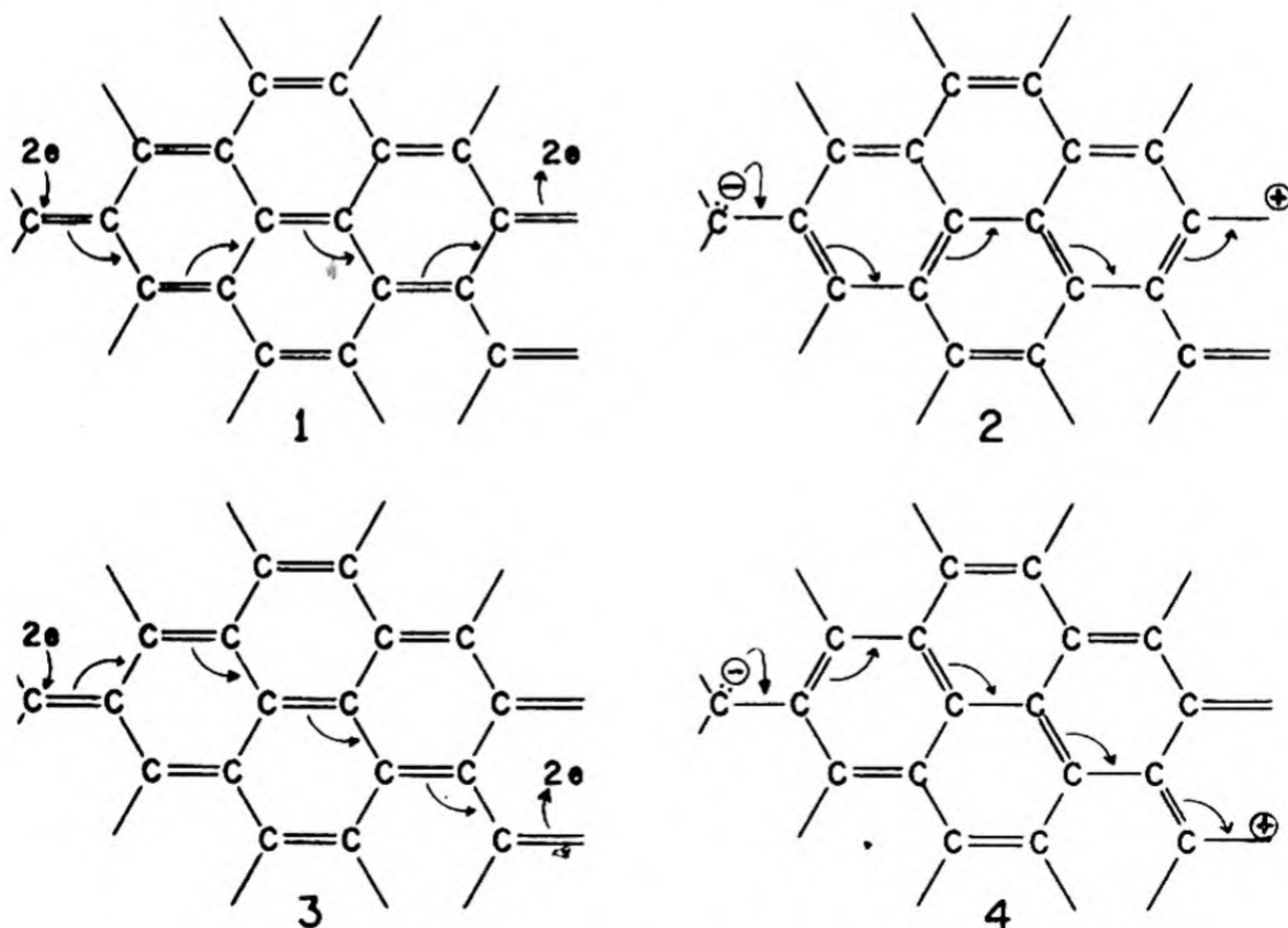
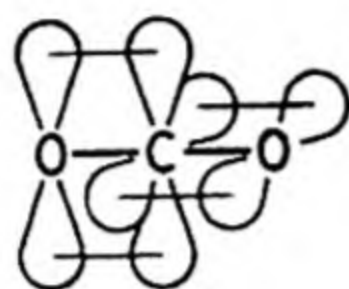
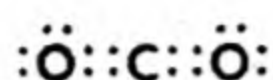


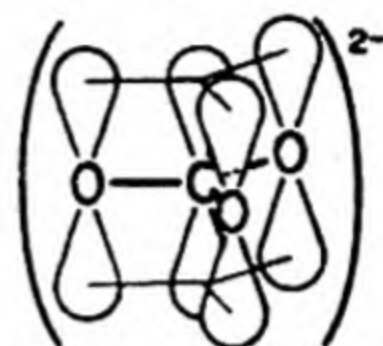
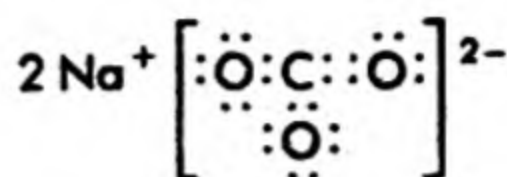
Fig. 4-25. Electron Transfer in Graphite.

carbon atoms is another important property. Many common compounds of carbon contain multiple bonds.

Double bonds



carbon dioxide

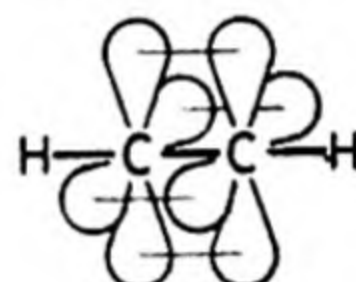


carbonates

Triple bonds

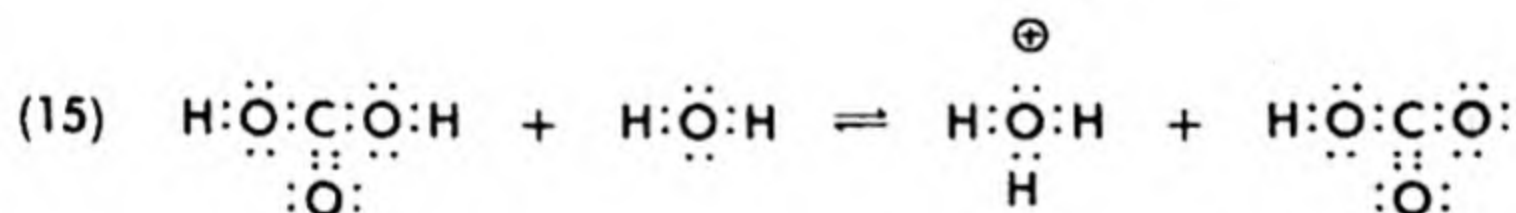
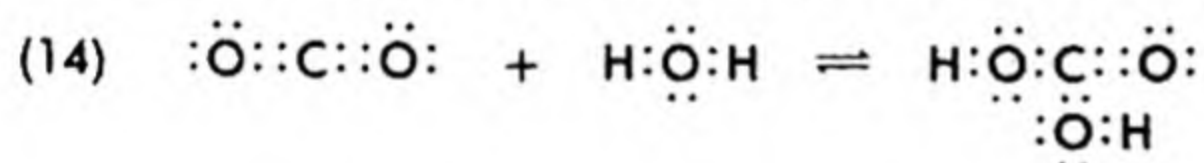


hydrogen cyanide

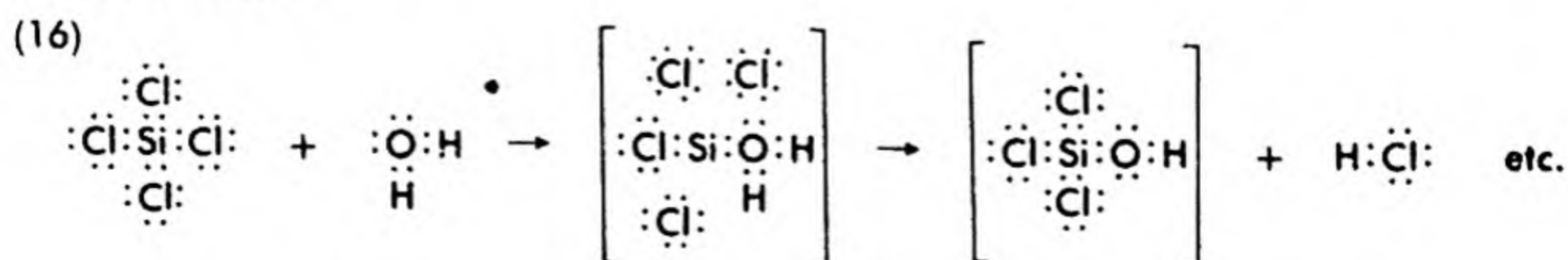


acetylene

Carbon dioxide is a covalent gas which dissolves in water to form a weak acid. Thus, the hydrous oxide of carbon is carbonic acid.



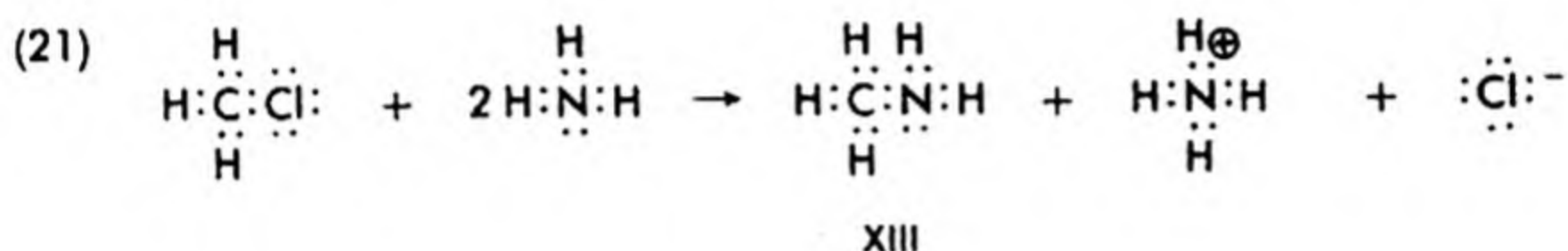
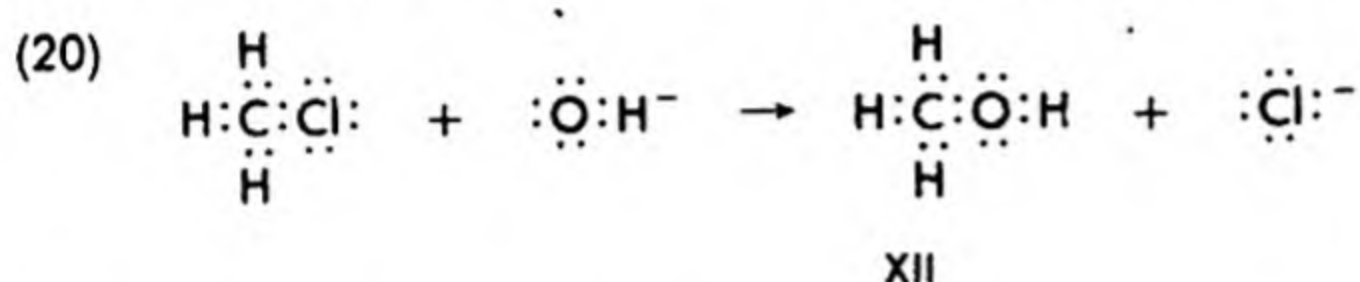
Carbon tetrachloride is a covalent liquid. Unlike silicon tetrachloride, phosphorus chlorides, and sulfur chlorides, it is not readily hydrolyzed by water. The difference is explained by the ease with which the Period 3 elements can expand their valences because of *d* orbital availability in these elements. Atoms of these elements can admit water molecules to their valence spheres until they hold as many as six covalent bonds before a single chloride ion is obliged to leave. The carbon kernel, on the other hand, must reject a chloride ion before or at the same time as the new bond is formed.



B. Bases

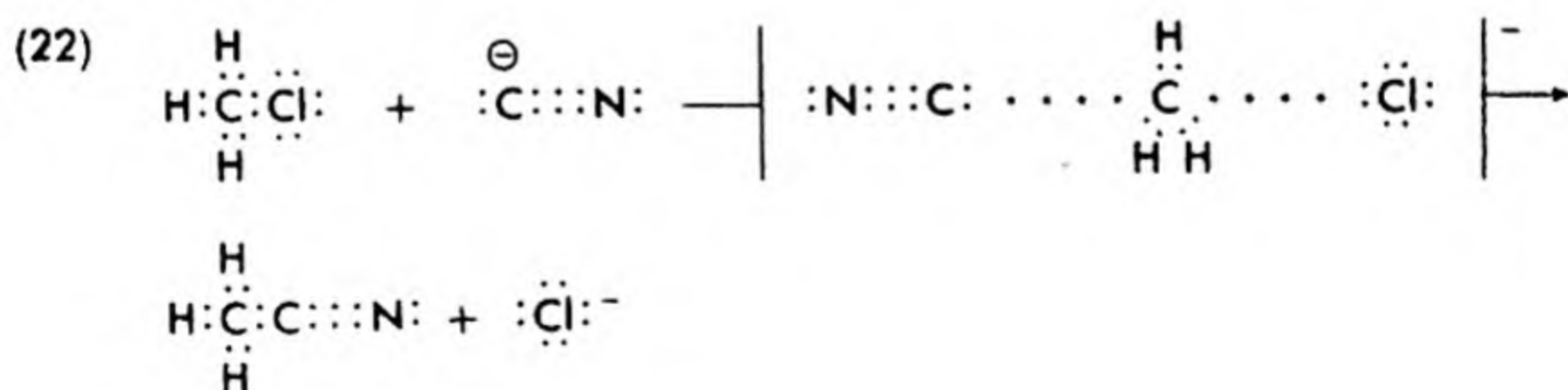
Many different bases are used in organic chemistry. Included, for example, are alkali metal hydroxides, carbonates, and bicarbonates. Sodium bicarbonate often has the advantage of being a source of high acid-neutralizing capacity but operating at relatively low pH. Nitrogenous bases, such as ammonia, generally serve as replacement agents.

Bases are also used extensively to replace easily displaced groups such as halogen atoms. Chlorides, for example, form alcohols, XII, and amines, XIII, by treatment with appropriate bases.



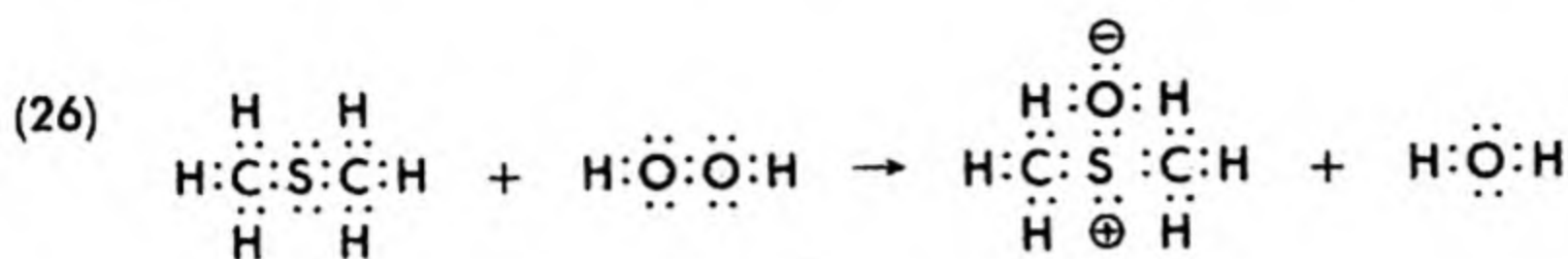
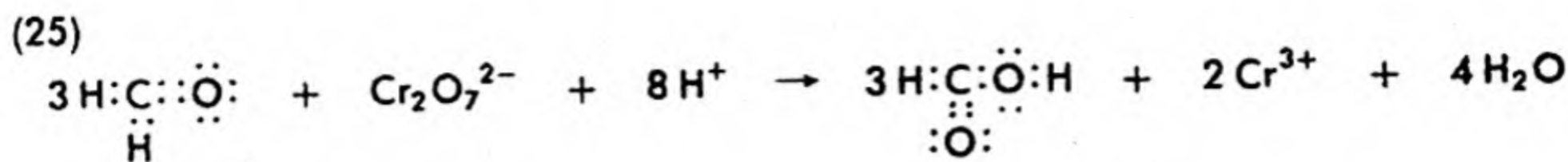
C. Other Replacing Agents

Many salts of weak acids are used to introduce groups into organic molecules in place of halogen atoms or sulfate groups. Some of the more useful of these are sodium cyanide, sodium sulfide, sodium nitrite, sodium salts of organic acids, and the corresponding silver or cuprous salts. Such salts act through unshared electrons, in turn displacing other atoms or groups with an electron pair. These reactions are sometimes reversible, the position of equilibrium depending on mass action, and are sometimes substantially irreversible, where the products are much more stable than the reactants.



D. Oxidation and Reduction

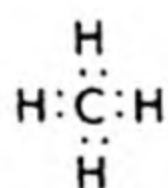
Oxidation is loss of electrons; reduction, gain of electrons. While many oxidation-reduction (redox) reactions involve a clear transfer of electrons from one atom to another, many, including most organic redox reactions, involve no obvious transfer of electrons.



(1) *Balancing Redox Equations.* There are two general methods for balancing redox equations. One is the oxidation number method. A newer method separates the oxidation from the reduction and shows the transfer of electrons. It is called the partial ion-electron method or half-cell method. Both methods are essential to a student's repertoire of skills, since neither by itself is effective in solving all problems of balancing. The student should refer to a general chemistry or analytical chemistry textbook (see Supplementary Readings at the end of this chapter) to review the general principles in full at this point. Failure to master oxidation-reduction reactions is a severe handicap to a student of organic chemistry. Oxidation number is the outgrowth of valence theories of the nineteenth century. The concept is retained, however, because of its usefulness in balancing oxidation-reduction equations. The oxidation number of an atom is the algebraic sum of its electronic charge and the polar charge values of its covalent bonds.

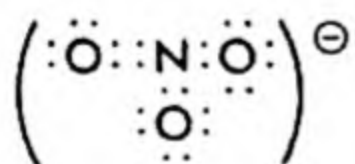
The formal electronic charge of an atom is found in principle by adding its kernel charge (positive), the number of unshared electrons in its valence orbitals (negative), and half the number of electrons shared by the atom (negative). It gives the approximate charge on an atom in an assumed structural formula.

Examples:



Carbon atom:

Kernel charge	+4
No unshared electrons	0
$\frac{1}{2} \times 8$ shared electrons	<u>-4</u>
Formal electronic charge	0



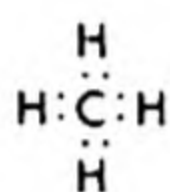
Nitrogen atom:

Kernel charge	+5
No unshared electrons	0
$\frac{1}{2} \times 8$ shared electrons	<u>-4</u>
Formal electronic charge	+1

In practice, the chemist soon learns to recognize the more common situations which involve formal charges from a count of the number of groups around certain atoms (compare ammonia, NH_3 , and ammonium ion, NH_4^+).

The sign of the polarity of a covalent bond is positive on an atom joined by the bond to an atom with a higher kernel charge or to one lower in atomic number and with the same kernel charge. The sign is negative on an atom joined by the bond to an atom with a lower kernel charge or to one higher in atomic number and with the same kernel charge. The polar charge is zero for a bond which joins the atom to another of the same element. The magnitude of the polar charge is the number of electron pairs in the bond. Note that the polarity ordinarily gives the sign of electron distribution in a molecule, but the numerical value derived is an artificial one and is useful only in oxidation-reduction calculations.

Examples:

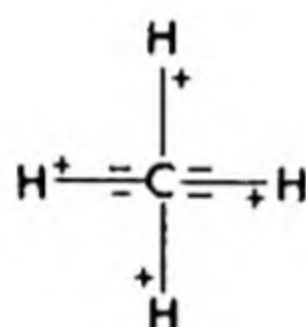


Carbon atom:

4 bonds alike:

Each bond = -1 (Kernel charge of hydrogen, +1, smaller than that of carbon, +4)

Total covalent bond polarity, $4 \times -1 = -4$

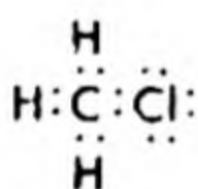


Each hydrogen atom:

1 bond only:

+1

(This is always true of hydrogen in compounds, except when the hydrogen is present as a hydride ion, H^- .)

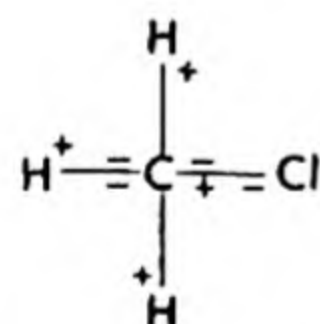


Carbon atom:

3 bonds alike to hydrogen, $3 \times -1 = -3$

1 bond to chlorine, $1 \times +1 = +1$

Total covalent bond polarities -2



Chlorine atom:

1 bond only:

-1

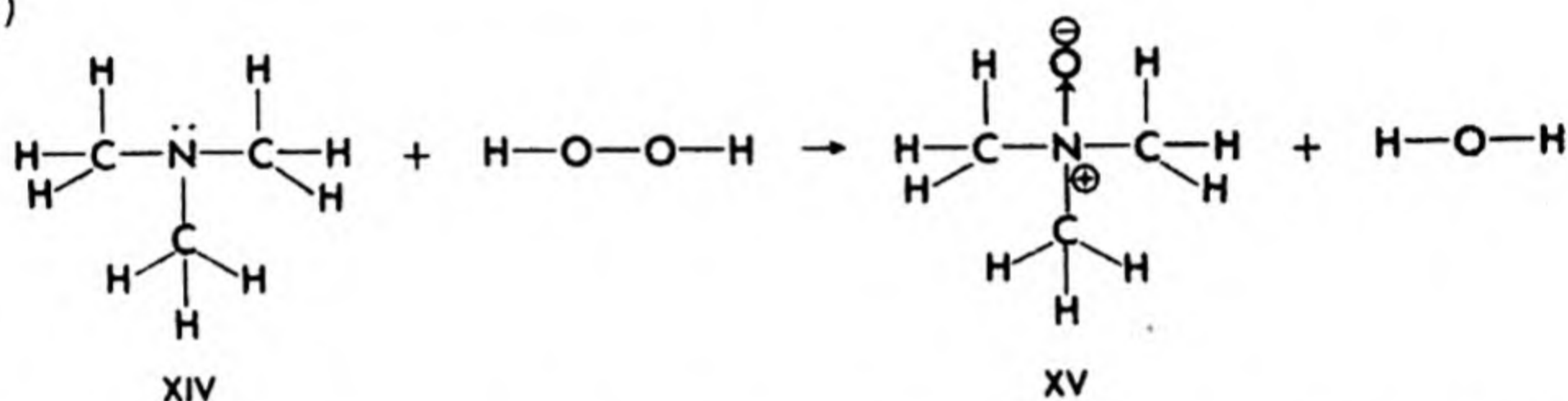
To find the oxidation number of an atom, its electronic charge and covalent bond polarities are added. The oxygen atom is an exception to the rule that the atom with the larger kernel charge is always negative in its covalent bond polarity. Even when attached to chlorine, bromine, or iodine, oxygen is arbitrarily considered negative.

While the concepts of formal electronic charge and of polar charge of a covalent bond have a considerable degree of artificiality, they are useful (in a limited sense) as measures of electron distribution in a covalent bond. For example, in the bond $\text{A}-\text{B}$ where the atom A has a lower kernel charge than B (i.e., is less electron-attracting than B), the actual charge

distribution usually has the same sign (i.e., $A^{\delta+}-B^{\delta-}$) as that which one derives by a consideration of the relative oxidation numbers of A and B. This implies that shared electron bonds are *not* in general equally shared between atoms, a concept of considerable importance in all areas of chemistry.

In many cases it may not be necessary to compute the total oxidation numbers of the oxidized and reduced atoms in order to balance a redox equation. In eq. (27), for example, most of the bonds to the oxidized nitrogen atom are unchanged, hence only the *difference* in oxidation numbers need be determined. This is done by ignoring the unchanged bonds and considering only the changes. Thus, the nitrogen atom, which in XIV

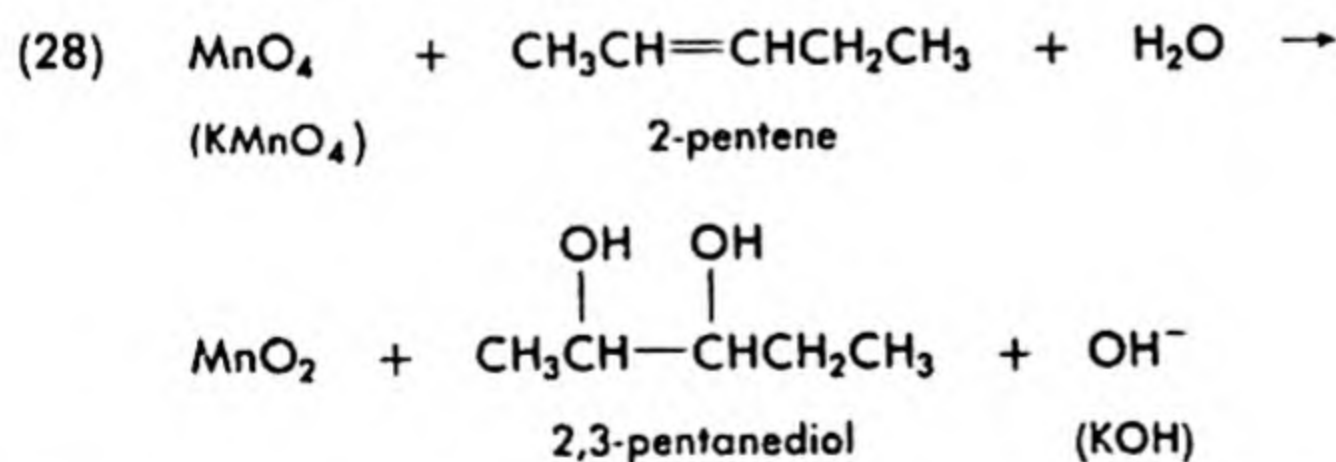
(27)



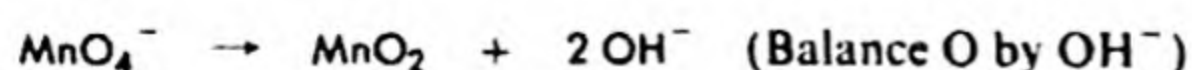
has no formal charge and an unshared electron pair (no covalent bond polar charge), has acquired a formal positive charge in XV and a polarity of +1 in the coordinate bond to the oxygen atom. The change in oxidation number is thus +2. The oxygen atoms in this example can best be handled by determining their full oxidation numbers, -1 in hydrogen peroxide and -2 in XV and in water.

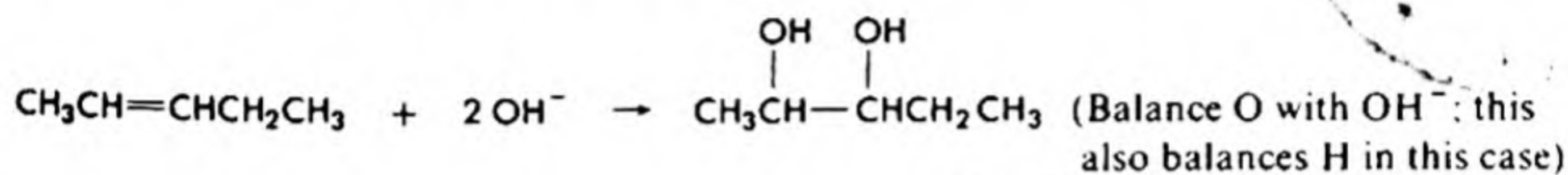
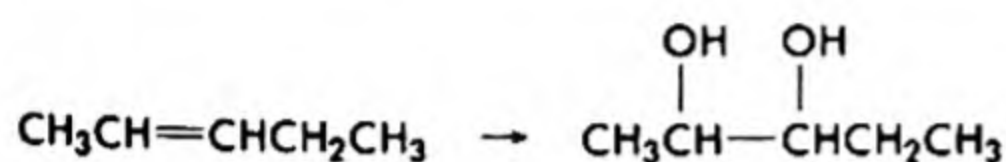
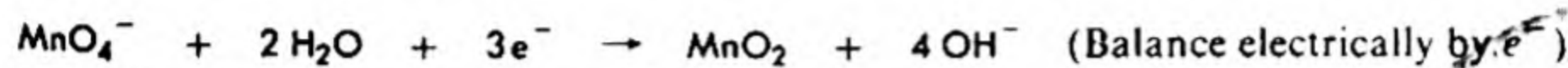
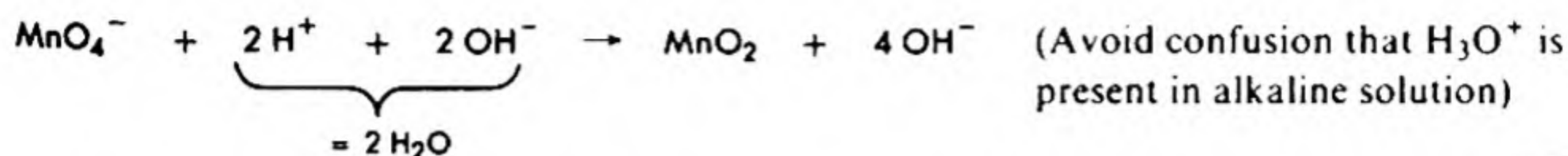
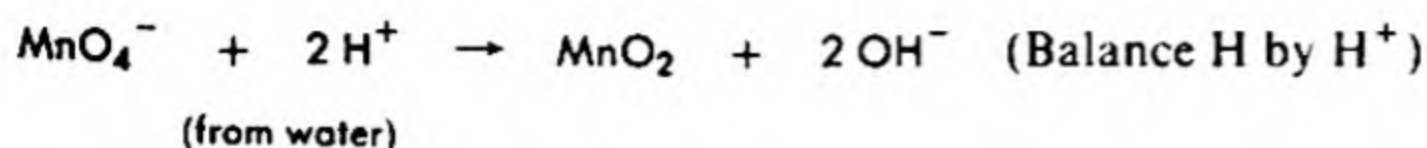
Some typical organic redox equations follow, balanced by methods most applicable to their particular environments.

Oxidation of 2-pentene by aqueous permanganate solution involves the following reagents and products:

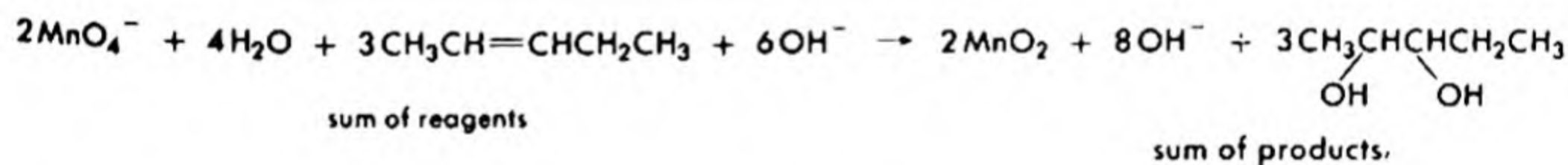
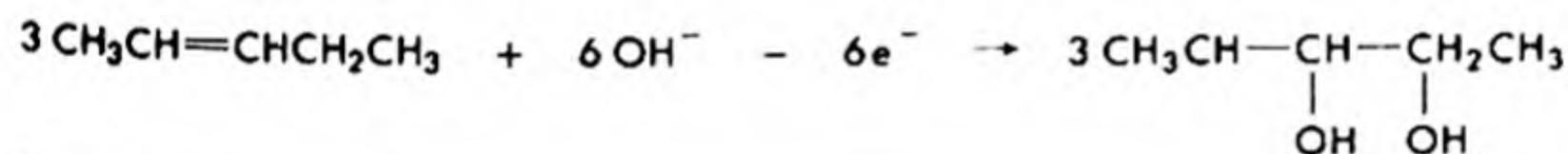
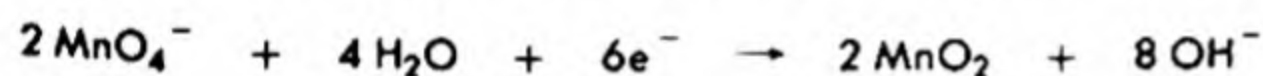


The reagents which undergo changes in oxidation number and their respective products are placed in separate half-cell (partial ion-electron) equations by the steps given below.

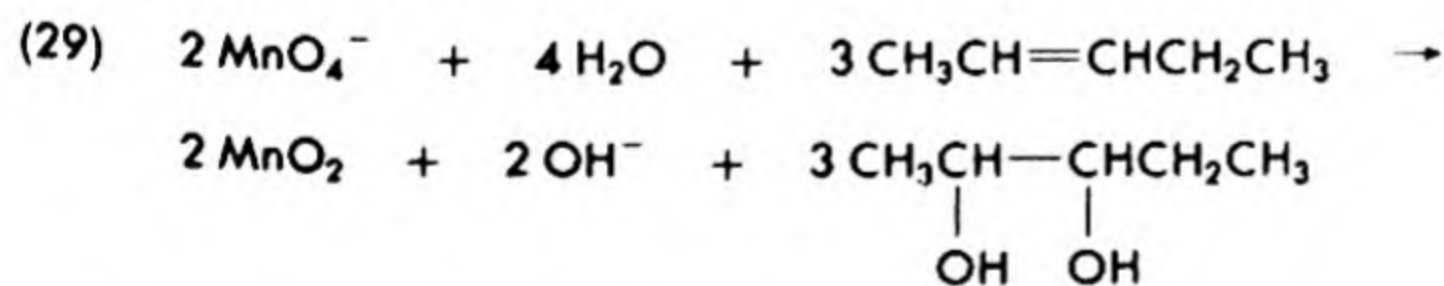




The gain of 3e^- per MnO_4^- and loss of 2e^- per pentene molecule must be equalized to a lowest common multiple *transfer* of 6e^- :



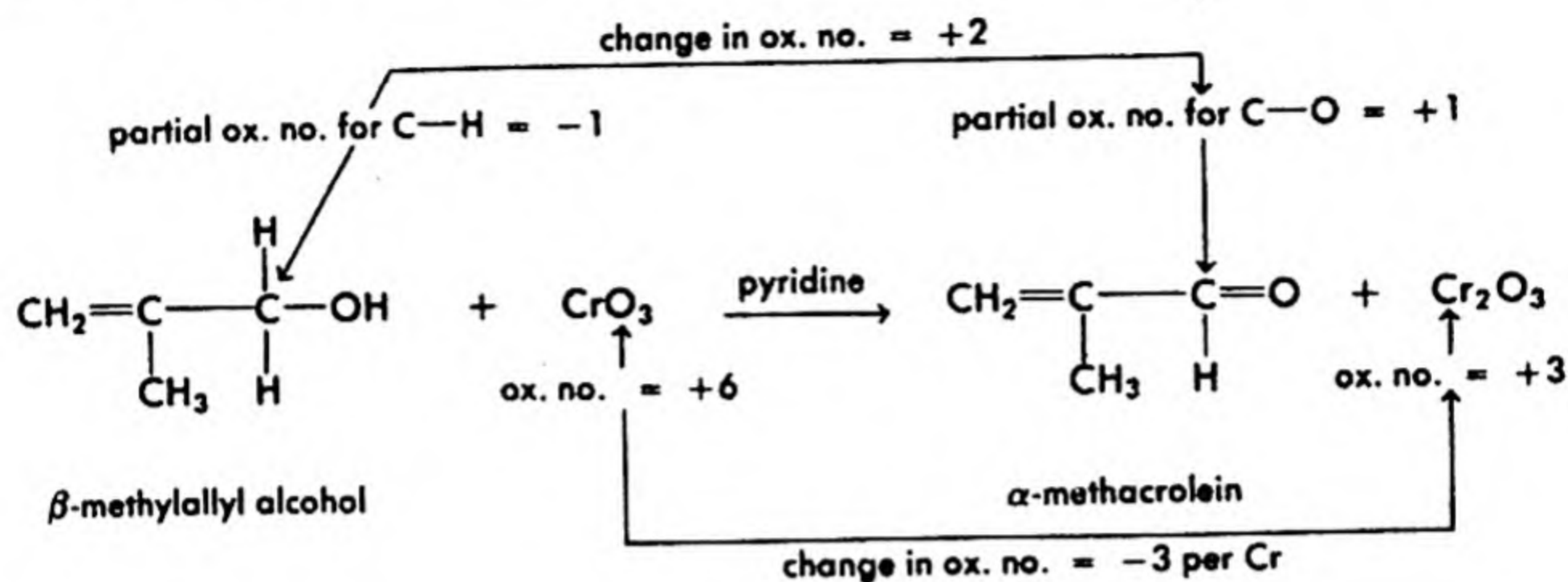
Cancellation of species which appear on both sides of the equation gives the net ionic equation.



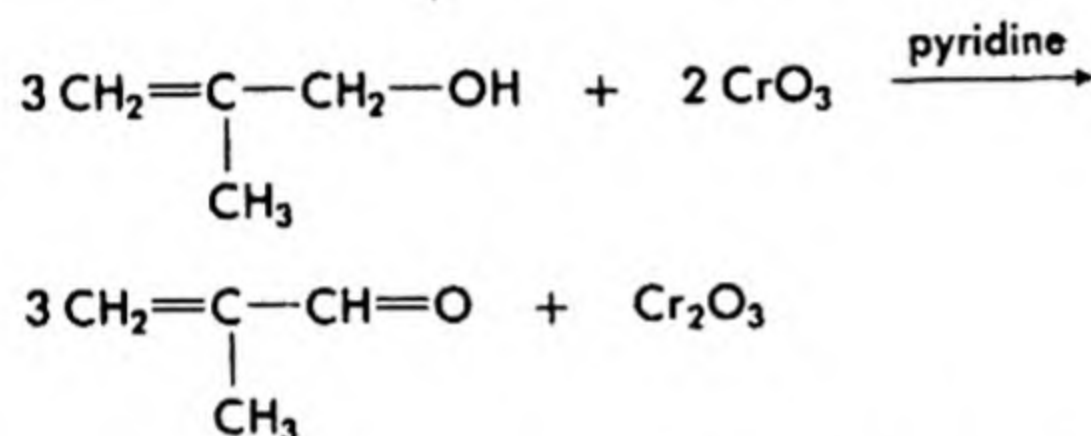
It may be noted that oxidation numbers were *not used at all* in this process; balancing utilized only the available substances and the principles of conservation of mass and of conservation of charge. Although hybrid methods are often taught, these may well be avoided in organic redox reactions, as mixing of oxidation numbers and half-cell equations involves the most difficult steps of both methods, and as such hybrid processes are likely to lead to confusion.

The oxidation of β -methylallyl alcohol to α -methacrolein does not

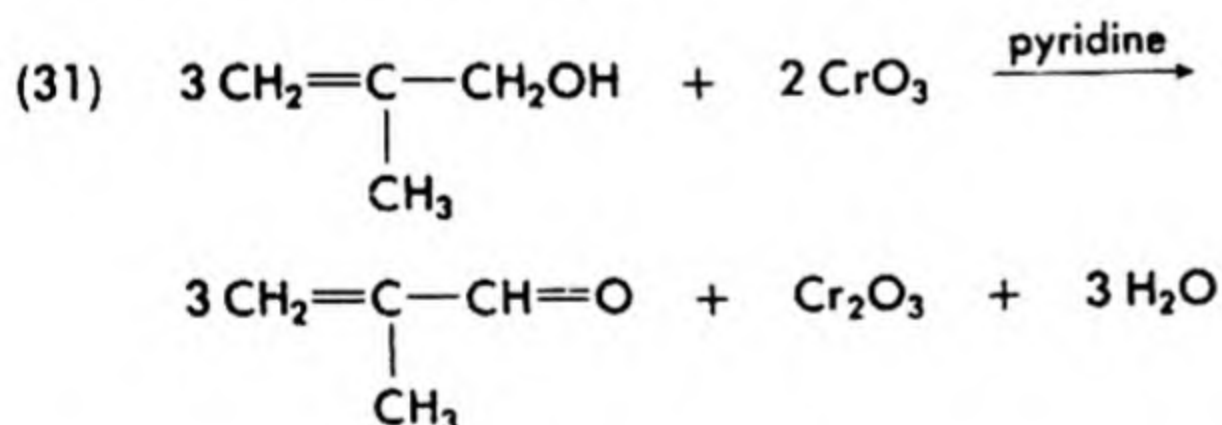
occur in aqueous solution; therefore, the oxidation-number method is more germane to this case.



Equalization of gains and losses in oxidation numbers gives:

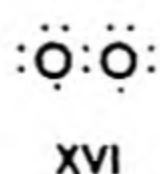


A count of atoms shows that 6H and 3O, that is, 3H₂O, are required as products. (No hydrogen or oxygen is produced.)



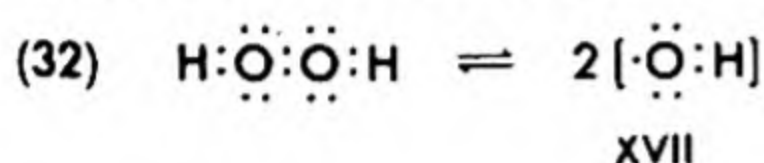
(2) *Oxidizing Agents.* The free halogens are strong oxidizing agents as a consequence of their high kernel charges and their resulting inclinations to seize electrons to form negative ions. Activity decreases from fluorine to iodine due to diminishing attractions of the larger sized kernels for electrons.

Oxygen and sulfur are less active than the halogens of the same periods. Nevertheless, oxygen is surprisingly reactive because its molecules exist in the odd-electron, or biradical, state, XVI. These biradicals, XVI, are more reactive than molecules in which atoms have inert gas configurations.

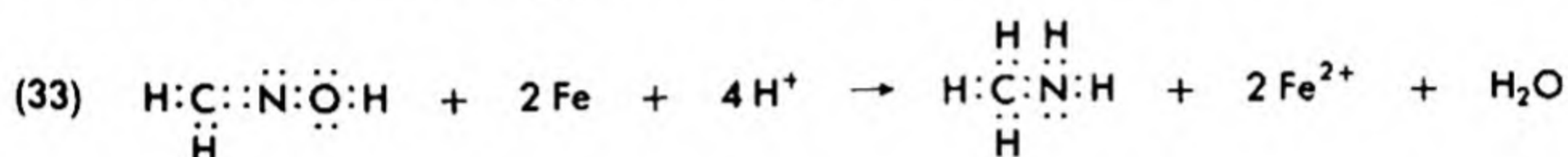


Many other oxidizing agents have strong electron affinities because of the crowding of many electron-seeking atoms, especially oxygen, into their molecules or ions. Examples are nitric acid, oxy acids of the halogens, chromic acid, dichromates, and permanganates.

Compounds which have oxygen-oxygen bonds, such as hydrogen peroxide and metallic peroxides, are also strong oxidizing agents. Often these reagents operate through the formation of free radicals, particles with unpaired electrons, XVII.

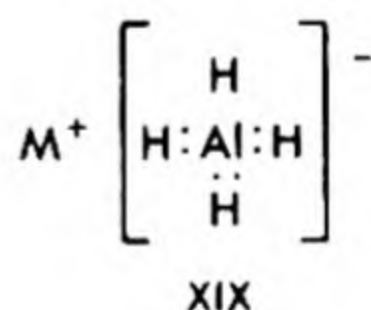
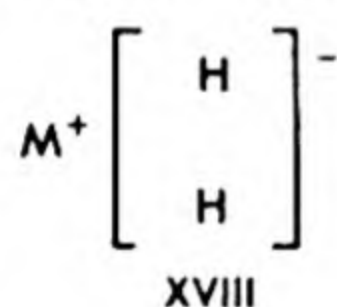


(3) *Reducing Agents.* Organic reactions use active metals primarily for their ability to reduce oxygen- or halogen-containing groups.



Probably first on the organic chemist's list of reducing agents is hydrogen. Although not very reactive in its molecular state, this gas is dissociated by platinum, palladium, and nickel into very active atoms (see eq. 23).

Other reducing agents of great utility are the borohydrides, XVIII, and the aluminohydrides, XIX, which are very powerful reducing agents, although selective in their action. These hydrides are reactive because their constituent atoms all are electropositive, hence form more stable bonds with electronegative elements.



SUPPLEMENTARY READINGS

- Bent, H. A., "Distribution of Atomic *s* Character in Molecules and Its Chemical Implications," *J. Chem. Educ.*, **37**, 616-624 (1960).
 Lambert, F. L., "Atomic and Molecular Orbital Models," *J. Chem. Educ.*, **34**, 217 (1957).

Balancing oxidation-reduction equations:

- Ayres,* G. H., *Quantitative Chemical Analysis*, Harper, New York, 1958, pp. 44-51.

* Contains full explanation of balancing equation by half-cell method.

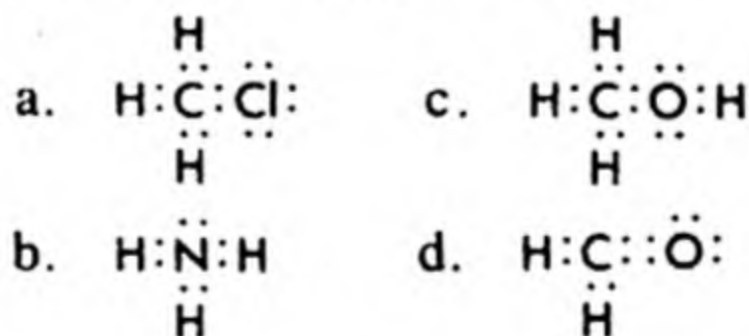
- Blaedel, W. J., and V. W. Meloche,** *Elementary Quantitative Analysis*, Row Peterson, Evanston, Ill., 1957, pp. 388-391, 701-704.
- Gregg,* D.C., *College Chemistry*, Allyn & Bacon, New York, 1961, pp. 212-216.
- Keenan, C. W., and J. H. Wood,*** *General College Chemistry*, Heath, Boston, pp. 195-200.
- Quagliano,** J. V., *Chemistry*, Prentice-Hall, Englewood Cliffs, N.J., 1958, pp. 369-382.
- Sienko, M. J., and R. A. Plane,*** *Chemistry*, 2nd Ed., McGraw-Hill, New York, 1961, pp. 113-114, 220-223, 295-297.
- Sisler, H. H., C. A. VanderWerf, and A. W. Davidson,** *General Chemistry*, 2nd Ed., Macmillan, New York, 1959, pp. 216-218.
- Taylor, M. D., *First Principles of Chemistry*, Van Nostrand, Princeton, N.J., pp. 312-316, 426-427.
- Willard,* H. H., N. H. Furman, and C. E. Bricker, *Elements of Quantitative Analysis*, 4th Ed., Van Nostrand, Princeton, N.J., 1956, pp. 94-96, 207-208.

QUESTIONS AND PROBLEMS

- Define and illustrate the following terms.

a. atomic orbital	f. electrovalence
b. bond angle	g. hybridization of orbitals
c. bond dissociation energy	h. hydrogen bond
d. bond distance	i. molecular orbital
e. covalence	j. polar molecule
- Describe a covalent bond in the following terms. Use as examples a single bond and a double bond.

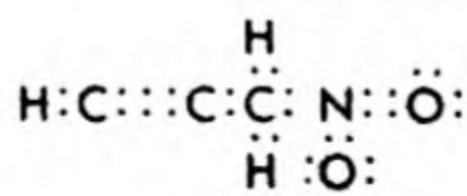
a. in terms of atomic orbitals	c. in terms of the energy content of a system of atoms
b. in terms of molecular orbitals	
- Tell which of the following pure compounds would be expected to form strong hydrogen bonds. Give the reasoning involved.



Write orbital diagrams for methanol, c, and formaldehyde, d.

- In the formula below, label the following:

a. simple covalent bonds	d. double bonds
b. coordinate covalent bonds	e. triple bonds
c. single bonds	f. unshared electron pairs



*Contains full explanation of balancing equation by half-cell method.

**Contains full explanation of balancing equations by valence number method.

***Contains explanations of balancing equations by both methods.

5. Explain why carbon can be expected by virtue of its atomic structure to share, not gain or lose, electrons.

6. Compute the formal electronic charge, covalent bond charge value, and oxidation number of each of the atoms below.

a. phosphorus atom in phosphoric acid

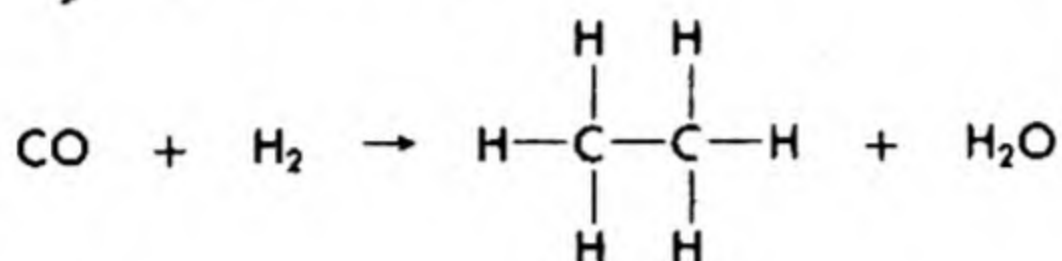
d. carbon atom in chloroform, CHCl_3

b. sulfur atom in sulfur dioxide

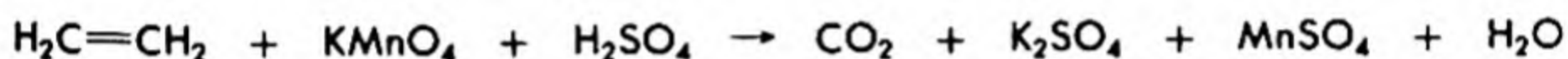
e. carbon atom in calcium carbide, $\text{Ca}^{2+}\text{C}\equiv\text{C}^{2-}$

c. sulfur atom in sulfuric acid

7. Balance the following equation by the oxidation number method.



8. Balance the following equation by both methods.



9. Draw the AO-MO energy diagram for the $\text{C}\equiv\text{C}$ bond in acetylene (§4-1G(3)).

UNIT



Fundamental Principles of Organic Structure and Classification

5

Constitution of Organic Compounds

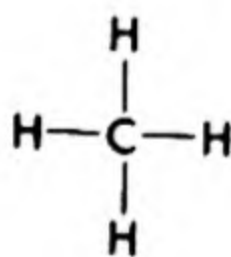
5-1. CARBON SKELETONS

The ability of carbon atoms to bond together in chains, rings, and complex forms was cited (§4-3A) as the basis of the vast number of organic compounds. The nature of the carbon skeleton, that is, the framework of carbon atoms in a molecule, has important consequences not only in the identity of a compound and its relationship to other compounds, but also in its chemical and physical properties.

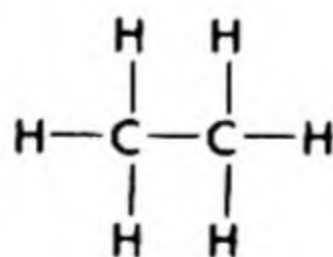
A. The Principle of Homology

A smooth gradation of chemical and physical properties is found in a series of compounds related by graduated differences in carbon chain lengths. Such a series, members of which have similar chemical functions and carbon chains which differ in the number of $\text{—CH}_2\text{—}$ (methylene) backbone increments, is called a *homologous series*. The compounds in the series are *homologs*. One important consequence of the principle of homology is that knowledge of the properties of a representative member of the series and knowledge of the general way the properties vary in the series are sufficient for knowledge of the properties of most members of the series.

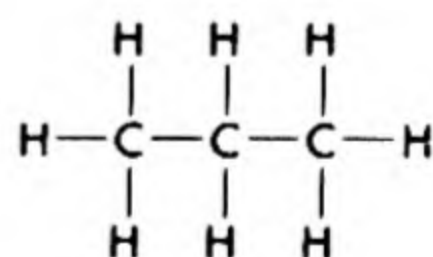
Part of a homologous series of hydrocarbons



methane

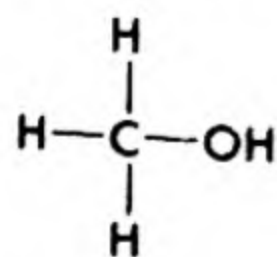


ethane

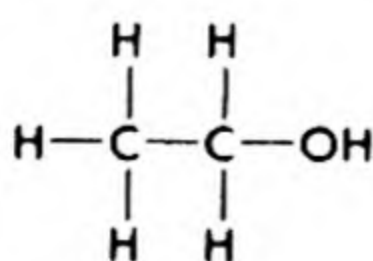


propane

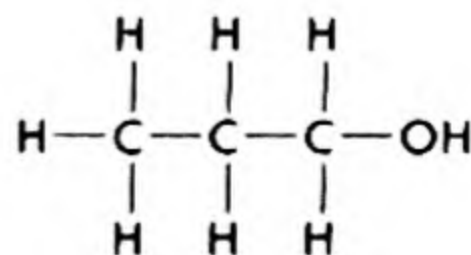
Part of a homologous series of alcohols



methanol



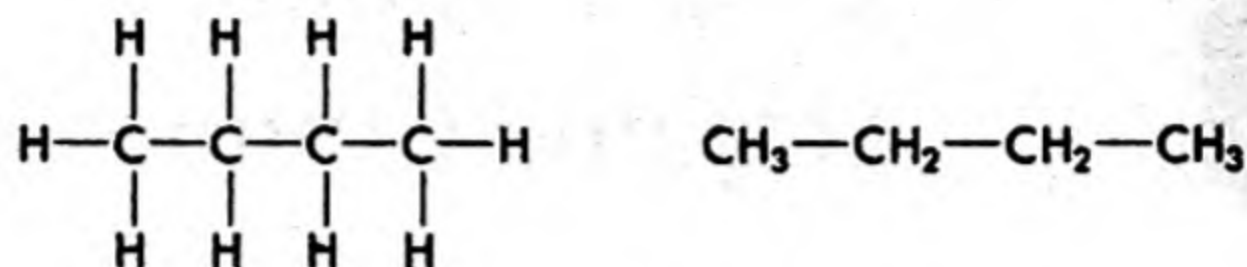
ethanol



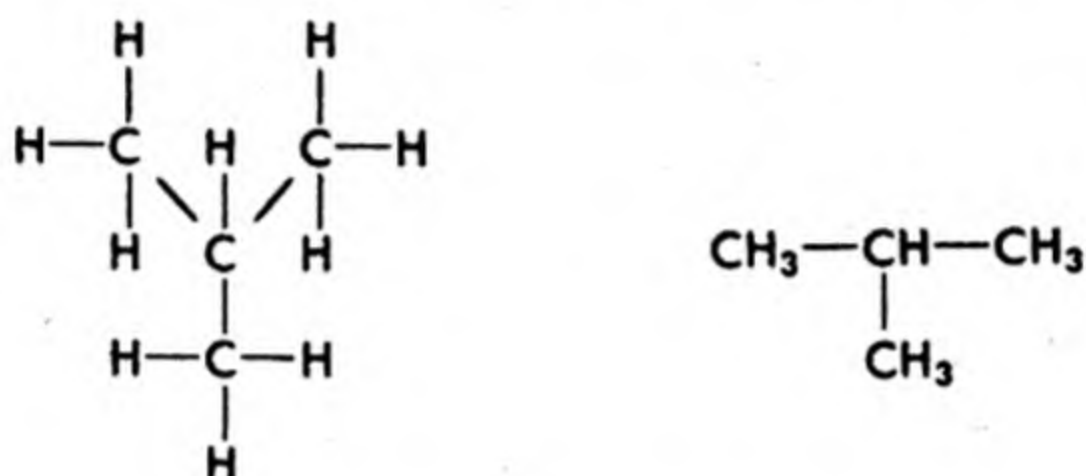
1-propanol

B. Continuous and Branched Chains

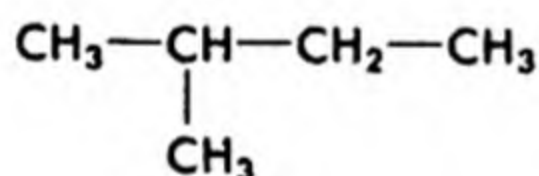
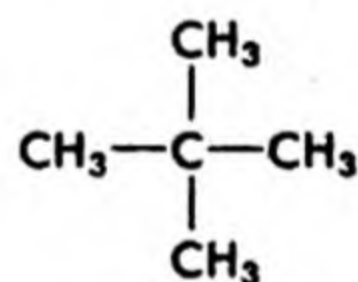
Carbon atoms may be connected in sequence to form compounds with *continuous* chains, as ethane and propane (above) and normal butane (*n*-butane).

normal butane, *n*-butane, or butane

However, since each carbon atom has a covalence of four, as many as four carbon atoms can be attached to another carbon atom to form *branched* chains, such as occur in isobutane, isopentane, and neopentane.



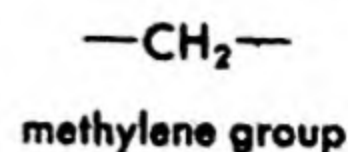
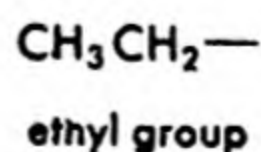
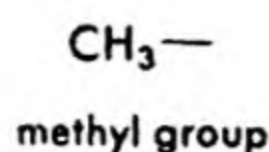
isobutane, 2-methylpropane

isopentane
2-methylbutaneneopentane
2,2-dimethylpropane

The multiplicity of such arrangements affords *skeletal isomers* or chain isomers (§3-2B).

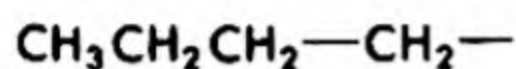
Compounds which have only hydrogen atoms attached to carbon skeletons are called hydrocarbons. If the carbon skeleton is a continuous or branched open chain, the hydrocarbon is called a *paraffin* or *alkane*. Such compounds as methane, ethane, propane, the butanes, and the pentanes are alkanes. Alkanes are major constituents in petroleum and natural gas. They are widely used as fuels and chemical raw materials.

A portion of a hydrocarbon molecule formed by removal of one or more hydrogen atoms is called a *group*. A group derived from an alkane is an alkyl group. Examples are the methyl group, ethyl group, and

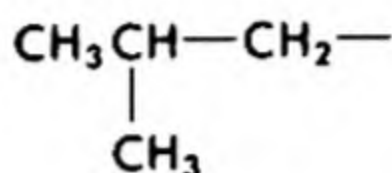


methylene group. A hydrocarbon group can be represented in general by $R-$ (from radical, an alternative name for group).

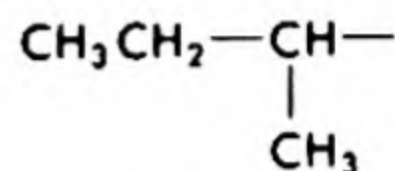
Alkyl groups are classified according to the number of carbon atoms attached to the incomplete or functional carbon as *primary* (RCH_2-), *secondary* (R_2CH-), and *tertiary* (R_3C-). In the preceding formulas, R represents component hydrocarbon groups.



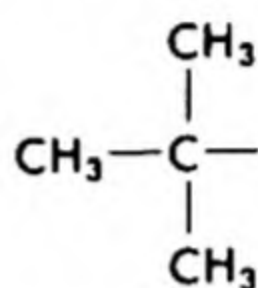
n-butyl
a primary group



isobutyl
a primary group



2°-butyl (sec-butyl)
a secondary group

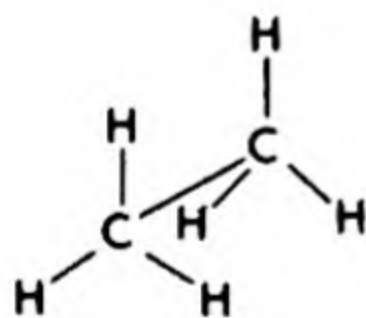


t-butyl (3°-butyl or tert-butyl)
a tertiary group

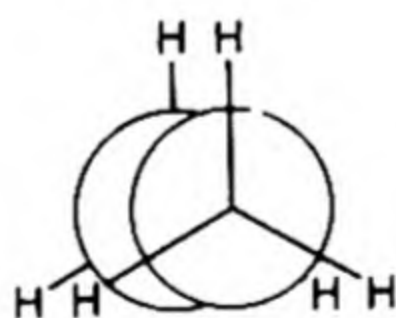
Together with alkanes, all other compounds with open (acyclic or ringless) chains are called aliphatic (Gk. *aleiphar*, fatty).

The various orientations which can be taken by organic molecules by simple twisting about the single bonds are called conformations (§3-2D). The ethane molecule is the simplest hydrocarbon molecule which can exist in different conformations. Certain idealized conformations are given names, as indicated below.

Sawhorse projections

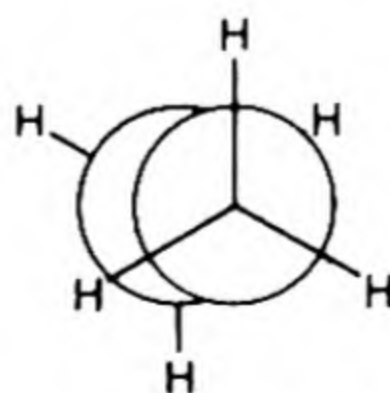
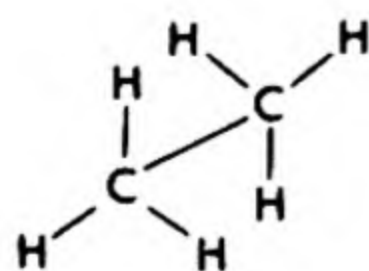
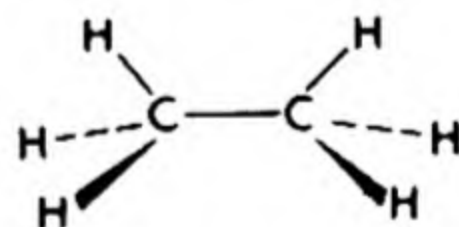


Modified Newman projections

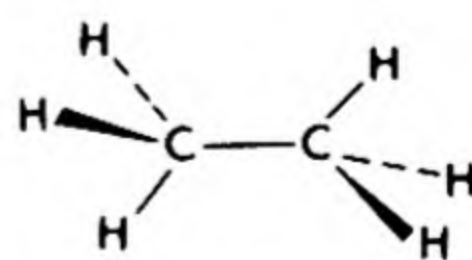


eclipsed conformation of ethane

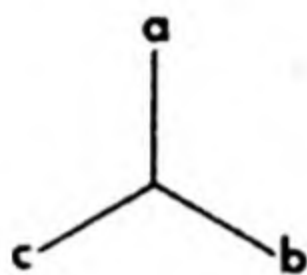
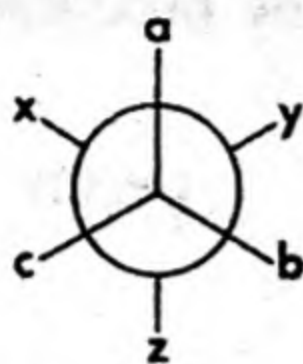
Conventionalized bond projections



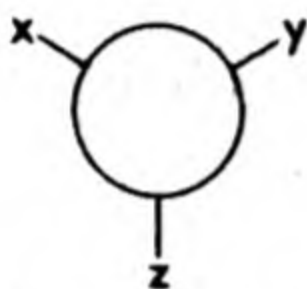
staggered conformation of ethane



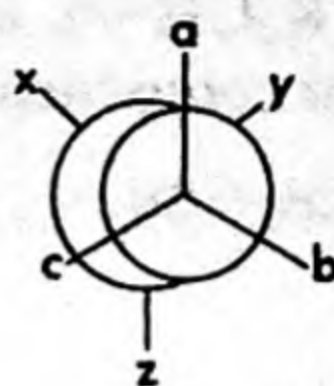
The relationships of groups in Newman projections and the modified Newman projections used in this text are as follows.

Newman projection

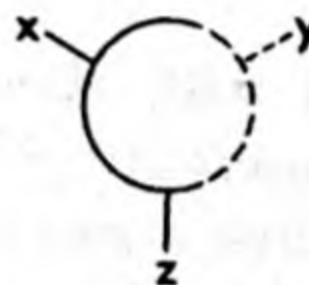
nearer carbon atom with groups a, b, c



farther carbon atom with groups x, y, z

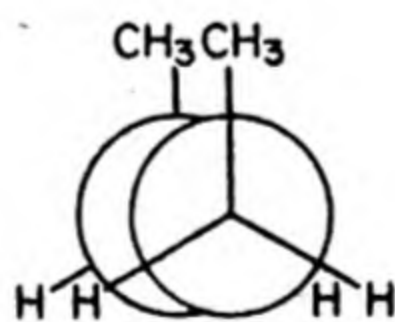
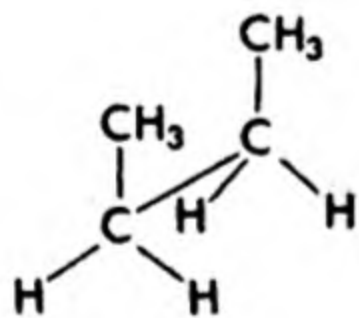
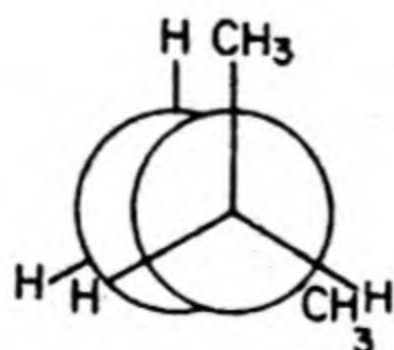
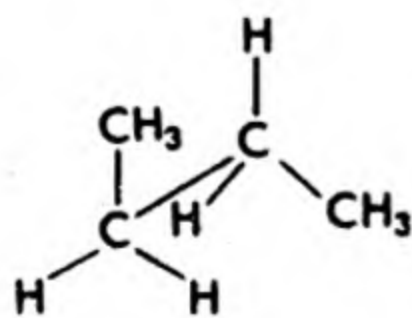
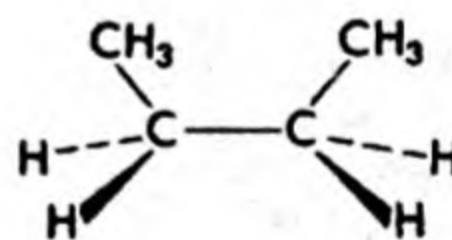
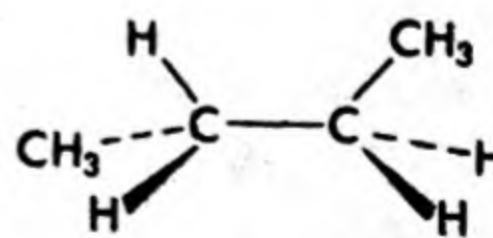
Modified Newman projection

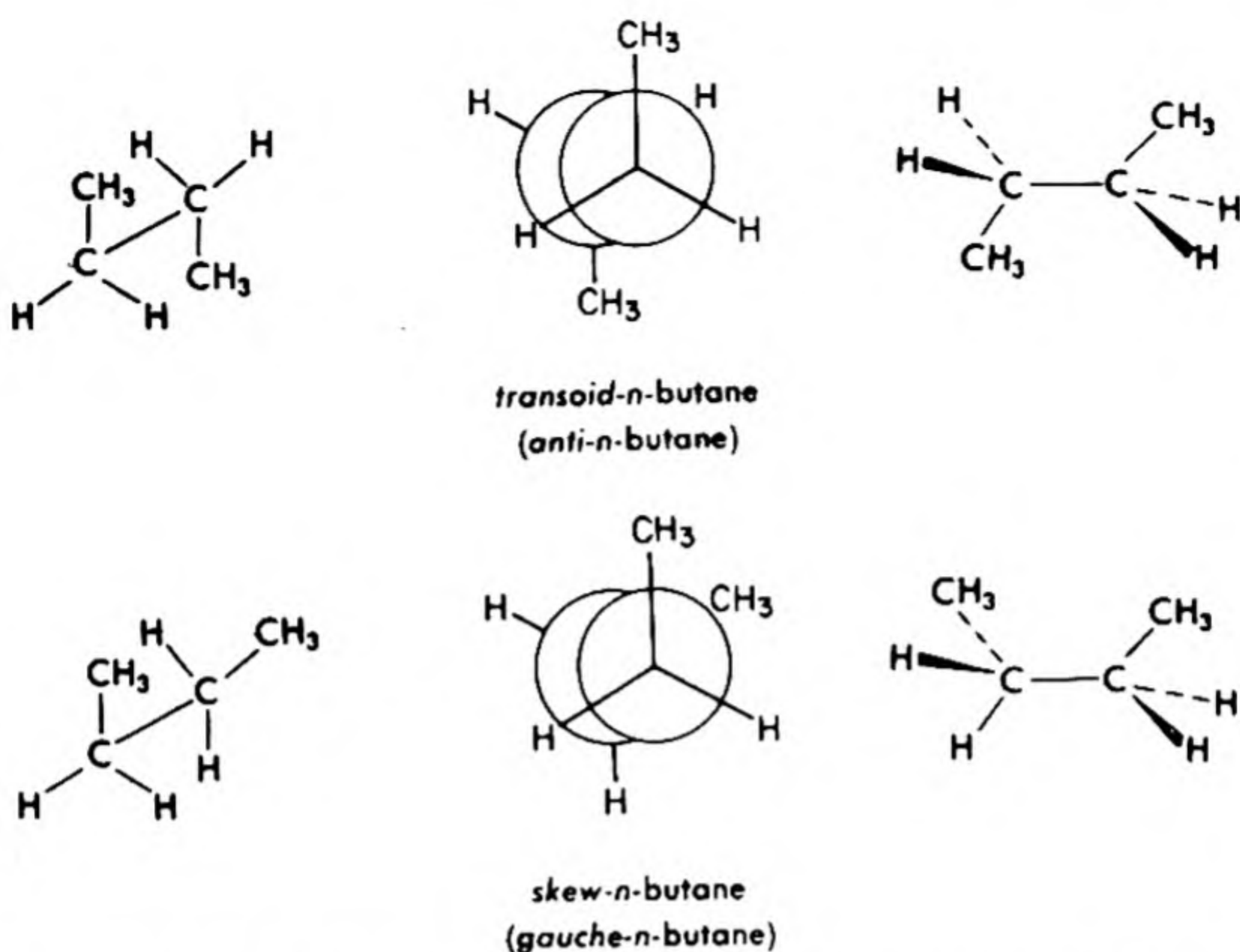
nearer carbon atom with groups a, b, c



farther carbon atom with groups x, y, z

A molecule such as butane is conformationally more complex. Consideration of conformations about only the two inner carbon atoms results in the following idealized descriptions.

*cisoid-n-butane**120° eclipsed n-butane*



Conformations of the external carbon atoms are comparable to those of ethane.

Between these idealized conformations exists an infinite number of other conformations. Not all are equally probable. Nonbonded interactions even between hydrogen atoms on adjacent carbon atoms produce a potential energy relationship, such as Fig. 5-1 for ethane, in which the energy content of the molecule is related to the *dihedral angle* between selected hydrogen atoms, one on each carbon atom. The dihedral angle is that observed between bonds, one to the front and one to the rear carbon

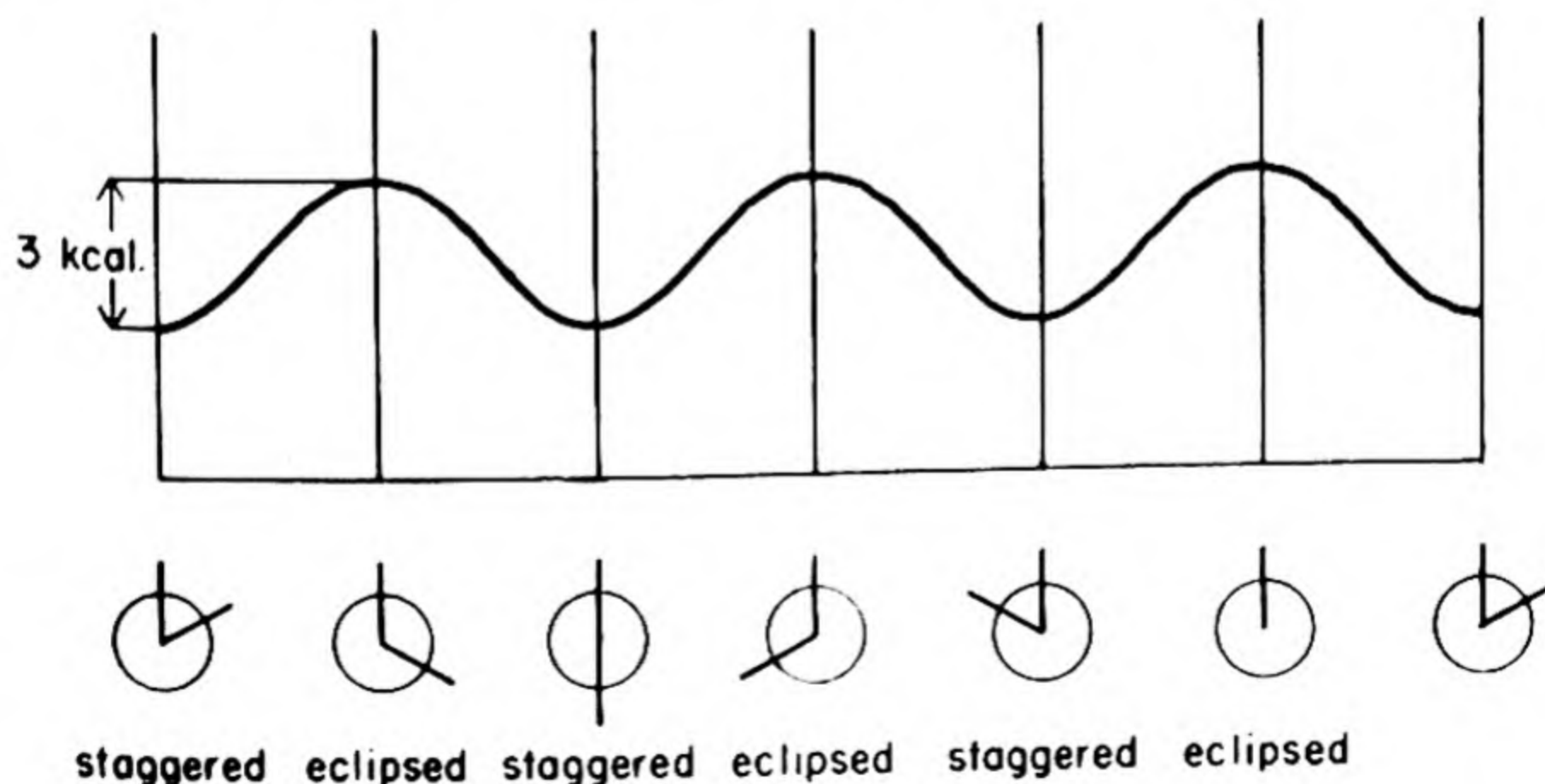


Fig. 5-1. Energy Diagram for the Rotation of Ethane.

atom, as seen in the Newman projection, looking along the C—C bond. In eclipsed ethane, the dihedral angle between nearest hydrogens is 0° (or 360°), and that between farthest hydrogens is 120° (or 240°). In staggered ethane, the dihedral angle between nearest hydrogens is 60° (or 300°), and that between farthest hydrogens is 180° . The potential energy diagram shows the eclipsed conformation to be least stable, the staggered conformation most stable, with a difference of about 3 kcal./mole. Since three hydrogens from one carbon interact with the three on the other, the energy difference between staggered and eclipsed conformations in ethane for each hydrogen-hydrogen interaction is about 1 kcal./mole.

The larger the atoms or groups on the adjacent carbons, the larger are the nonbonded interactions; thus (Fig. 5-2) *skew-n-butane* differs from

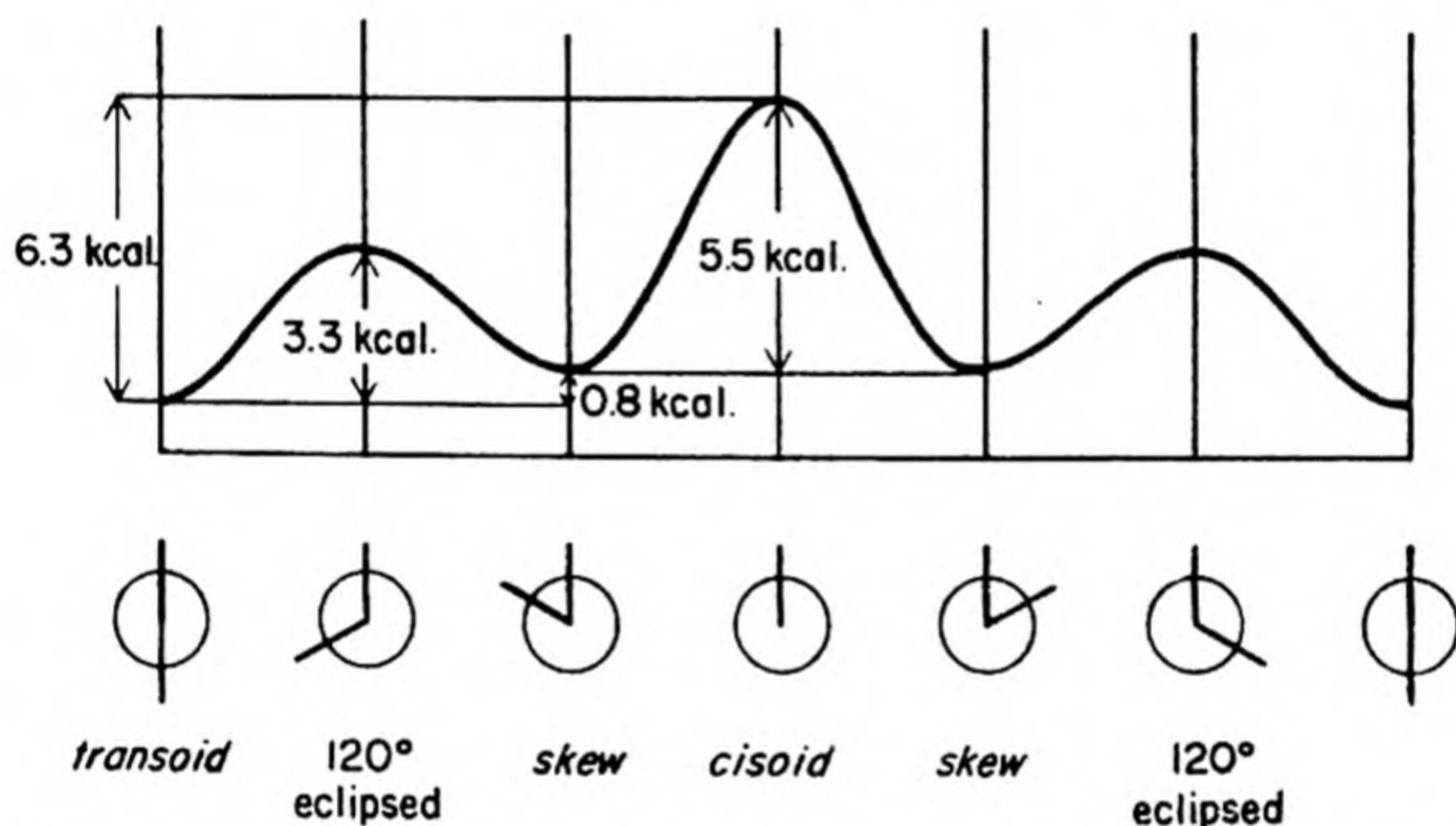


Fig. 5-2. Energy Diagram for the Rotation of *n*-Butane about the Center Carbon-Carbon Bond.

cisoid-n-butane by 5.5 kcal./mole, and *transoid-n-butane* from 120° eclipsed *n-butane* by 3.3 kcal./mole. Upon consideration of the H-H interactions and the number of CH₃-H or CH₃-CH₃ interactions, it can be shown that CH₃-H nonbonded interactions are about 1.2 kcal./mole and CH₃-CH₃ nonbonded interactions about 3.5 kcal./mole. The slight difference between *skew* and *transoid* conformations, about 0.8 kcal./mole, indicates that large groups interact with each other to some extent even at a dihedral angle of 60° .

The energy differences between conformations are not large enough to prevent rotation at usual temperatures. The ethane molecule contains as its total energy of translation, rotation and vibration 5.4 kcal./mole at 20° , so that the required energy for rotation is easily available. Similarly, rotational energy barriers of other alkanes are readily available from kine-

tic and internal energy contents. Thus, separate conformers (or rotamers, conformers which differ by simple rotation), *skew* and *transoid*, cannot be isolated from alkanes under conditions such that the molecules are gaseous or liquid. But rotation is not completely free; the more stable conformations are preferred.

A long carbon chain can assume many conformations. Certain ideal ones are found under special conditions. If the adjacent methylene groups in a long chain are all *transoid*, the molecule has a zigzag conformation. This is the usual conformation of crystalline pure normal paraffin hydrocarbons and many other continuous-chain organic compounds. On the other hand, if an all-*skew* conformation is assumed, the carbon chain takes a helical conformation (Fig. 5-3).

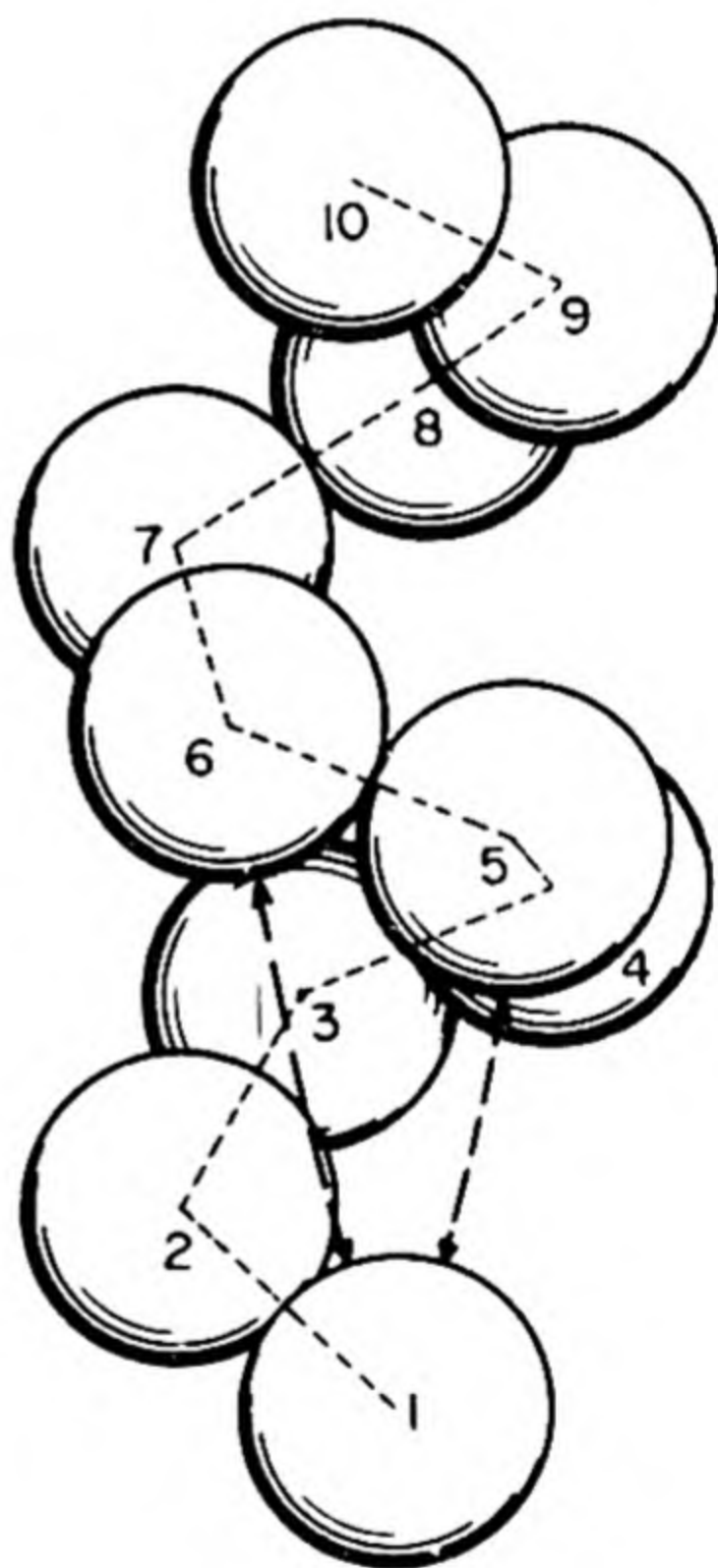


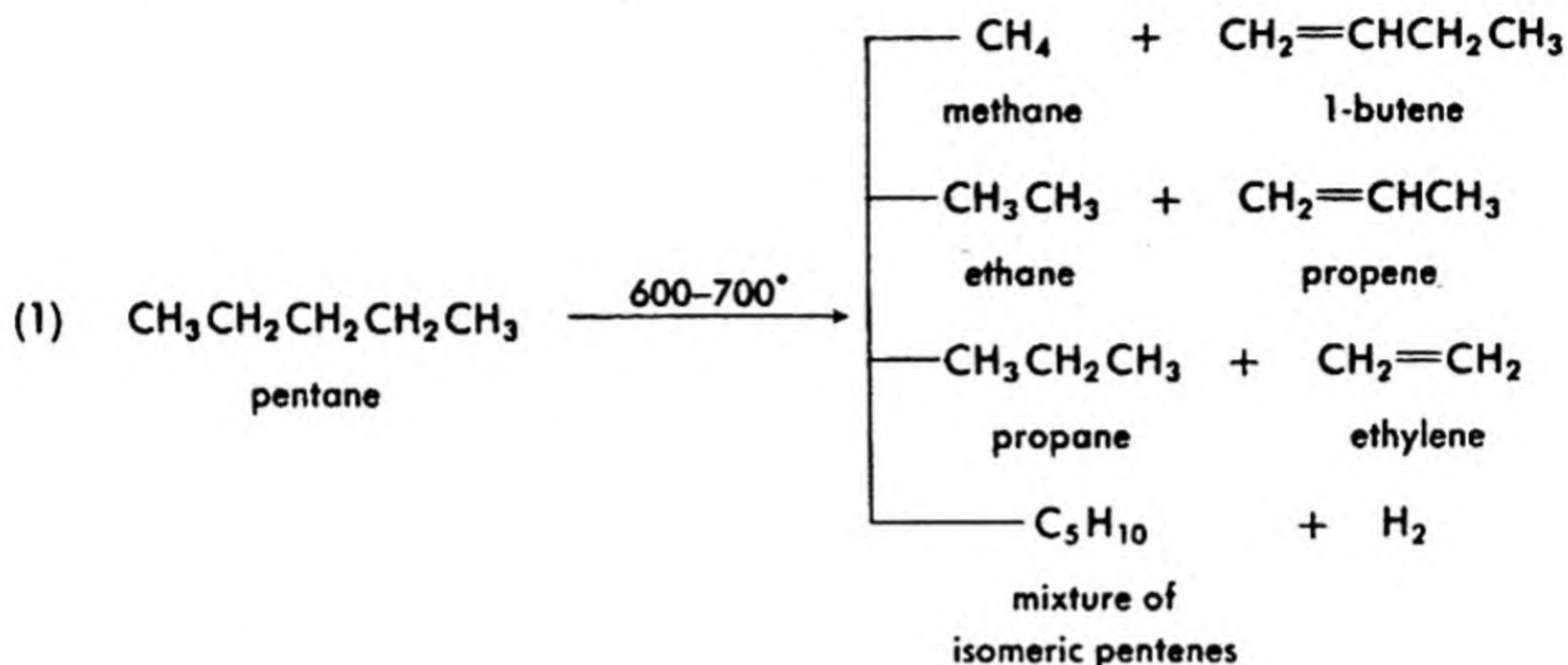
Fig. 5-3. A Coiled Chain of Atoms.

C. Multiple Bonds

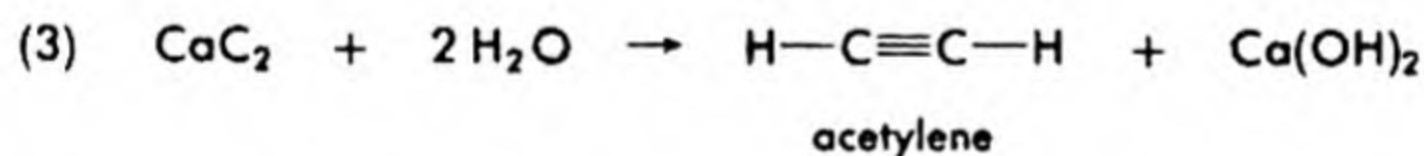
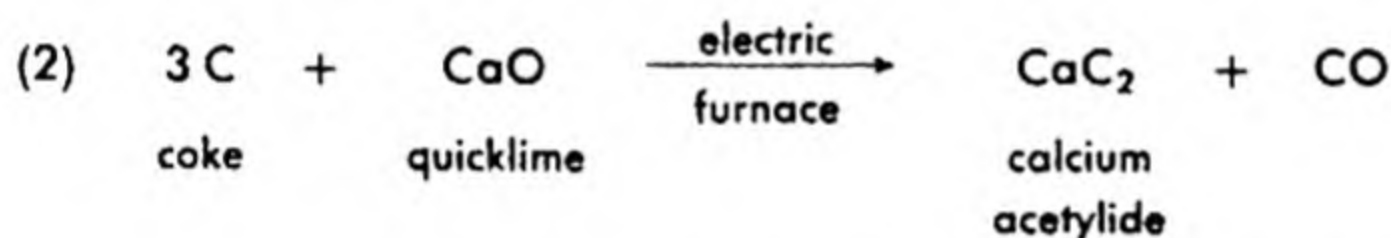
Carbon chains can contain double and triple bonds (§4-1G(3)). Compounds with such bonds are called *unsaturated*, since they readily add hydrogen to form *saturated* compounds. The latter cannot add hydrogen without cleavage of C—C bonds.

Hydrocarbons with double bonds are *olefins* or *alkenes*. Since the double bond has marked effects on chemical properties, it is considered a

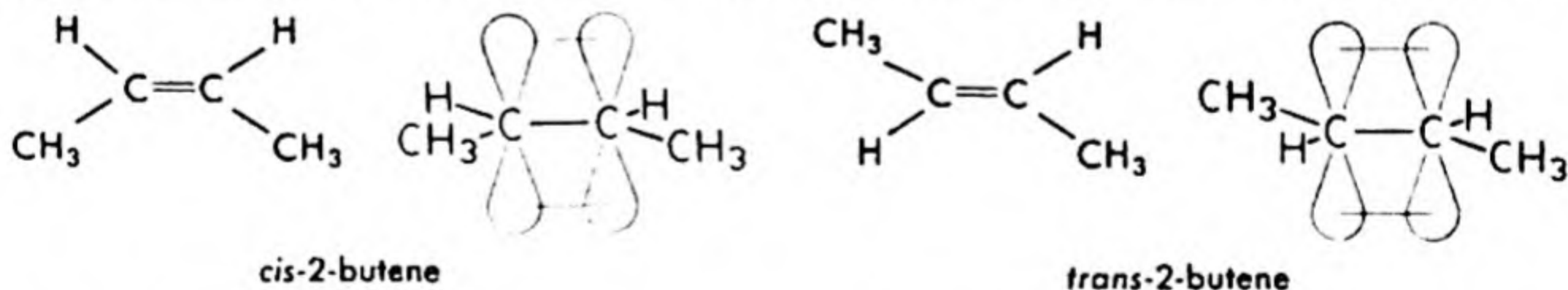
functional group. Alkenes are formed industrially by cracking of petroleum fractions. In this process, large molecules are broken down to smaller molecules (outline 1).



The triple bond which occurs in *acetylenes* or *alkynes* is also a functional group. Only the lowest homolog, acetylene, is commercially very important. It can be prepared from elementary carbon, hence is of classical interest as an intermediate in the total synthesis (i.e., from the elements) of organic compounds.



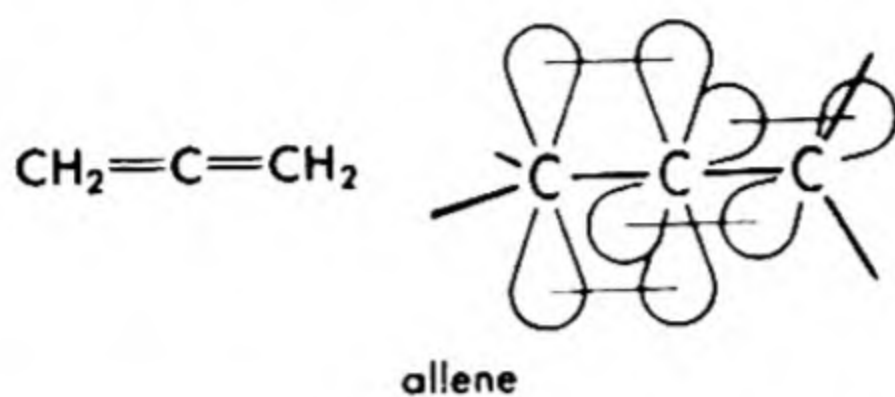
The difficulty of rotation about a double bond (§4-2B) makes possible the separation of *geometric isomers* such as *cis*-2-butene and *trans*-2-butene. Such isomers are also called *cis-trans* isomers. The potential



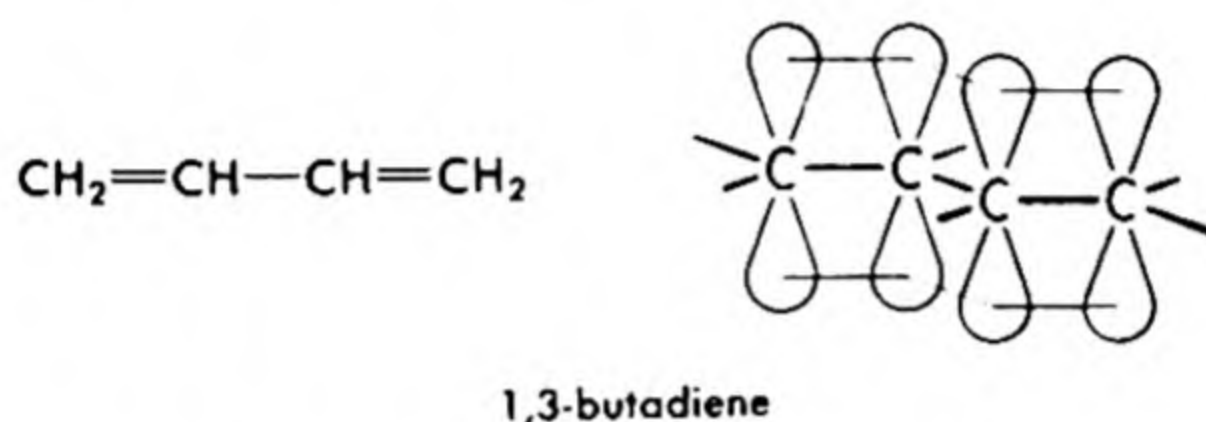
energy barrier between these isomers, 62 kcal./mole in the pure *cis* compounds, larger in the *trans*, is sufficient to prevent rotation about the double bond at a measurable rate below 250°.

When rotation is promoted by a catalyst, it is found that *trans*-2-butene is the more stable isomer (by about 1 kcal./mole) due to larger methyl group interactions in the *cis* isomer. The greater stability of *trans* isomers is common, but not universal.

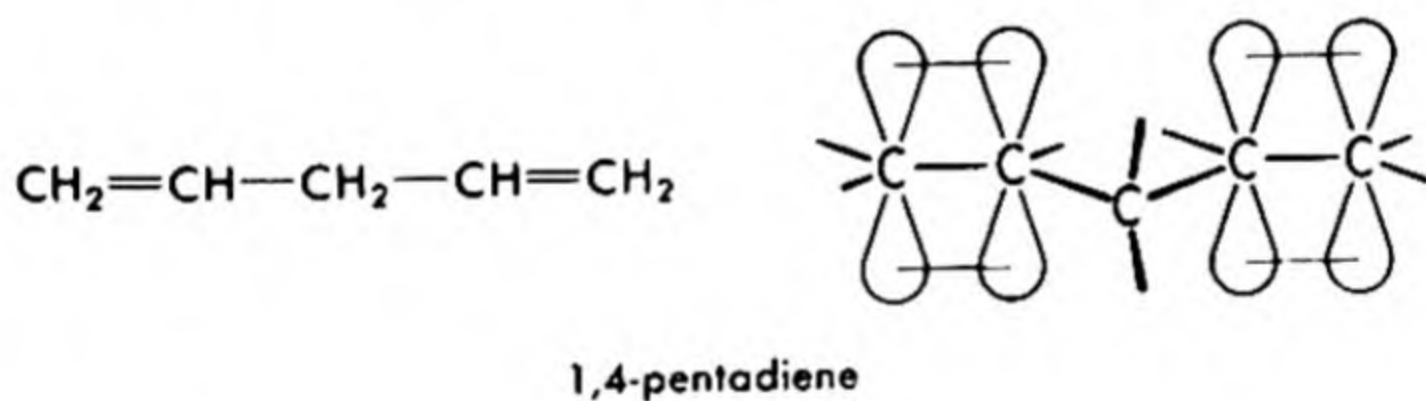
When several double bonds occur in a molecule, three types of arrangements are recognized, depending on the relative positions of the double bonds. Those with two double bonds at the same carbon atom, such as



allene, are called *cumulated* systems. Those with alternating double and



single bonds, such as butadiene, are called *conjugated* systems. Those with



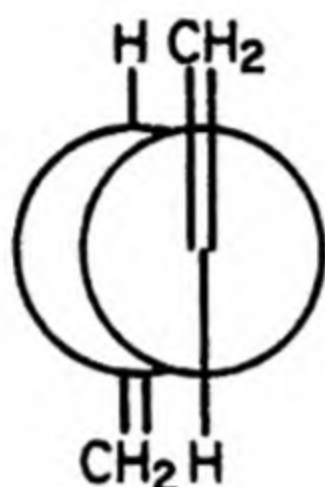
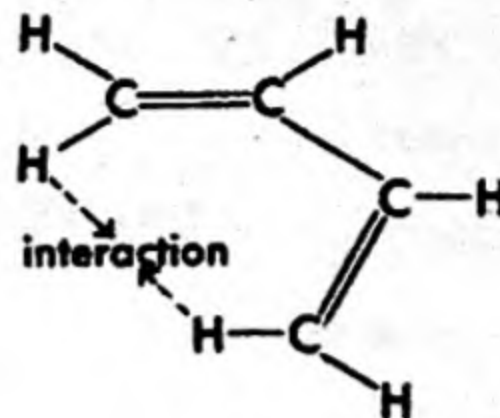
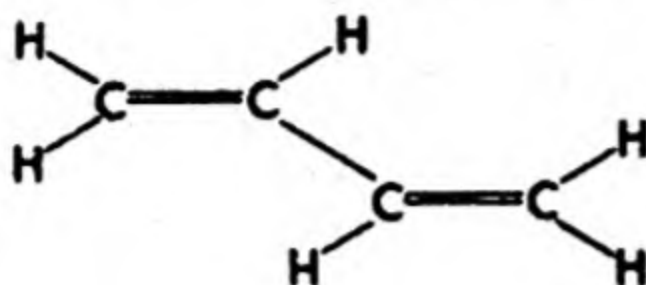
double bonds separated by two or more single bonds, such as 1,4-pentadiene, are called *isolated* systems. Conjugated systems are characterized by possible overlapping of π orbitals across the formal single bonds. Such overlapping is impossible in cumulated systems and isolated systems.

The central carbon atom in a cumulene (cumulated hydrocarbon) has *sp* or digonal hybridization. Thus, the two double bonds are linear. However, the π orbitals are at right angles to each other on the axis of the bonds. This can result in a different kind of geometric isomerism called optical isomerism (§31-2). The isomers are nonidentical mirror images of each other, or *enantiomorphs*, like a right hand and a left hand. One pure

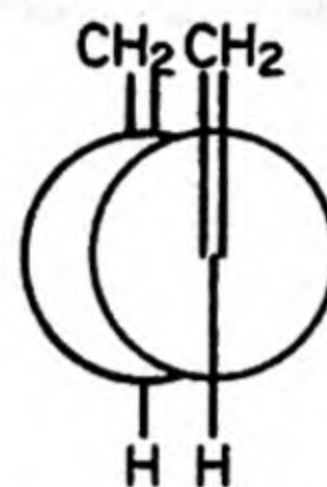


isomer rotates plane-polarized light to the right or clockwise (dextrorotatory), the other to the left or counterclockwise (levorotatory).

The butadiene molecule has two preferred conformations, the *transoid* or *s-trans* (single bond *trans*), and the *cisoid* or *s-cis*.



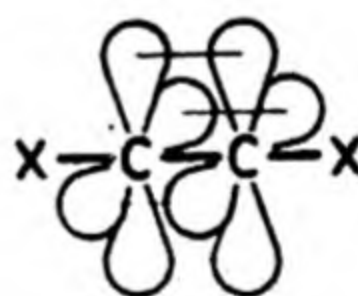
s-trans-1,3-butadiene



s-cis-1,3-butadiene

In both of these conformations, some overlapping of the π orbitals across the C—C single bond can occur. The *s-trans* conformation is more stable than the *s-cis* by 2.3 kcal./mole, partly due to interaction between two of the terminal hydrogen atoms in the *s-cis* form.

Triple bonds involve two *sp*-hybridized carbon atoms, so that three adjacent bonds are linear.



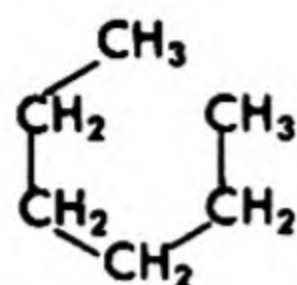
Since any rotatable groups at X are too far apart for nonbonding interactions, and since the two π orbitals screen any interactions that operate through the bonding system, complete freedom of rotation occurs at these positions. Thus, dimethylacetylene is a linear molecule with no rotational barriers.



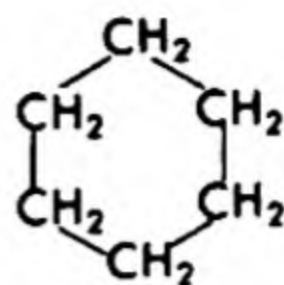
dimethylacetylene
2-butyne

D. Rings

When carbon atoms form a closed linkage of atoms, as in cyclohexane, they are said to form a *ring*. Compounds which contain rings are cyclic.



hexane (acyclic)

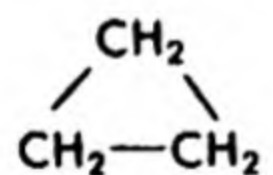


cyclohexane (cyclic)

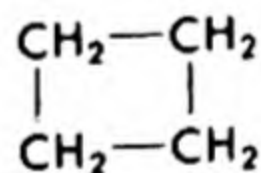
(No conformational information is intended)

Cyclic compounds are classified, from chemical considerations, into small-, medium-, and large-ring compounds. The exact ring sizes in each category vary with the property under discussion. For the present purpose, the historical classification of three- and four-carbon rings as small, five- and six-carbon rings as medium, and larger rings as large is appropriate.

It should be apparent that 109.5° bond angles between carbon atoms in small rings are impossible (Fig. 5-4). The bonding orbitals must be bent or distorted, or the bond hybridization must differ from tetrahedral, or both. Actually, the best compromise between bent bonds and less favorable hybridization than tetrahedral is obtained, with the result that some increase in energy content of the molecule can be ascribed to a small ring. For cyclopropane, with 60° bond angles, the "strain energy" is 28 kcal./mole or 9 kcal./Avogadro's number of bonds. For cyclobutane, with 90° bond angles, the strain energy is 26 kcal./mole or 6.5 kcal./Avogadro's number of bonds. As we shall see, this internal "strain" or potential energy affects chemical properties of small ring compounds.

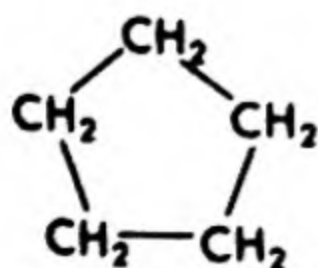
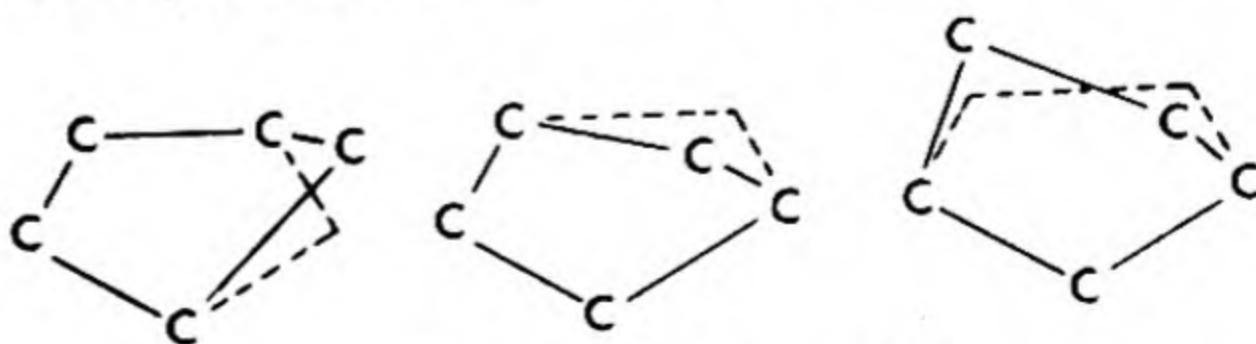


cyclopropane



cyclobutane

The cyclopentane ring, if planar, has ring bond angles of 108° , very nearly the tetrahedral angle, so that ring strain should be negligible. However, a planar conformation requires an all-eclipsed conformation for hydrogen atoms and other external groups. The minimum nonbonding interaction in a planar ring involves ten hydrogen-hydrogen interactions, or about 10 kcal. of eclipsing strain (also called torsional or Pitzer strain). Actual cyclopentane has only 6.5 kcal. of strain energy, indicating that the

cyclopentane
planarcyclopentane rings, some bent
conformations

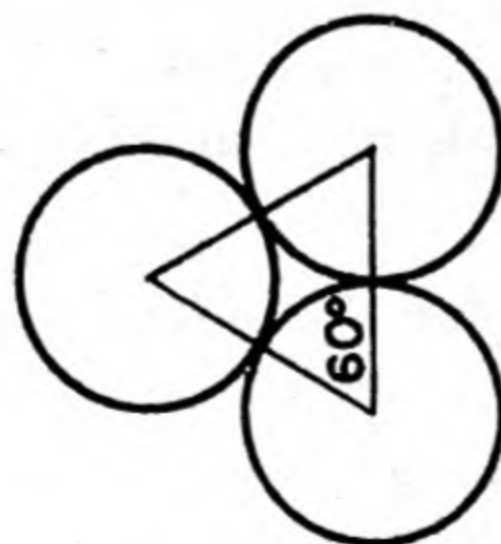
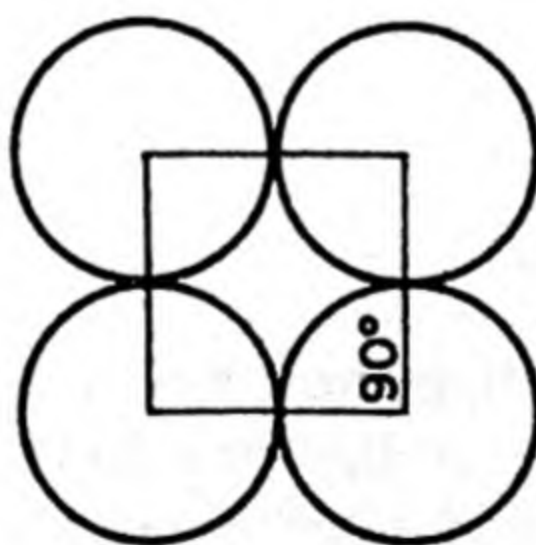
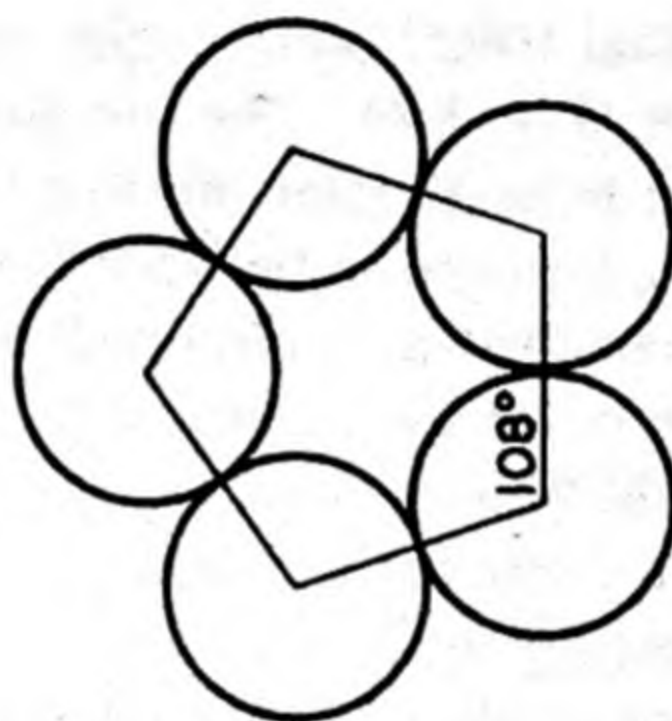
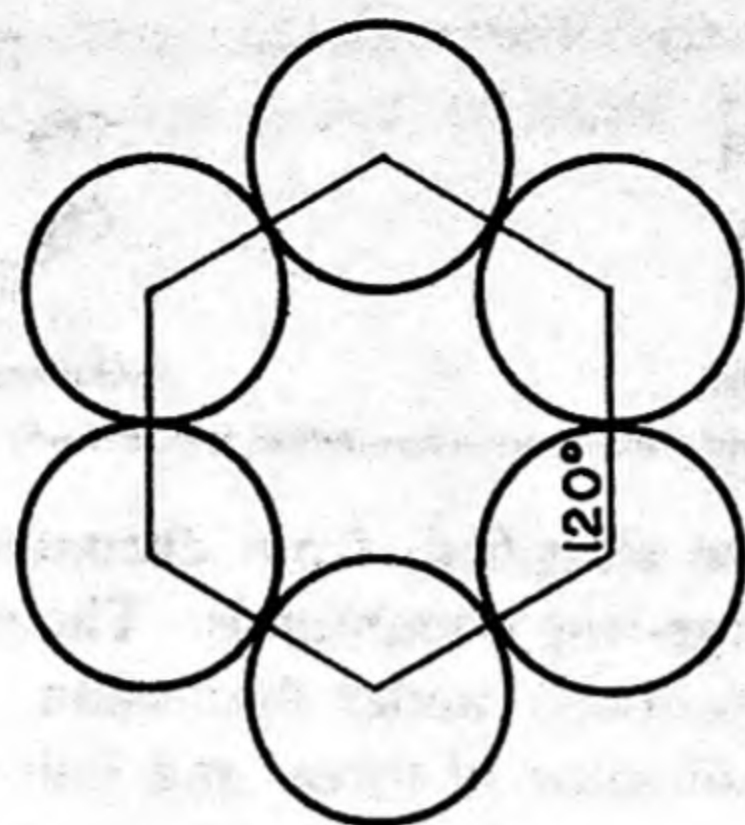


Fig. 5-4. Bond Angles in Planar Cyclic Hydrocarbons.

molecule has found a better balance between eclipsing strain and such ring strain as is produced by slight bending or puckering of the ring. That is, the best conformation for cyclopentane is a slightly puckered ring. Such bending is not static, but is considered to move in waves about the ring, since the energy barriers between different puckered forms are no more than 4 kcal./mole.

Rings larger than five-membered would also show ring strain if they were planar, as Adolph von Baeyer first thought (1885). Needless to say, such rings can bend or pucker (Fig. 5-5) even more easily than cyclopentane to produce, in general, essentially strainless rings. Consideration of the conformations and their energies in cyclohexane gives a fairly representative, as well as important, illustration of such effects.

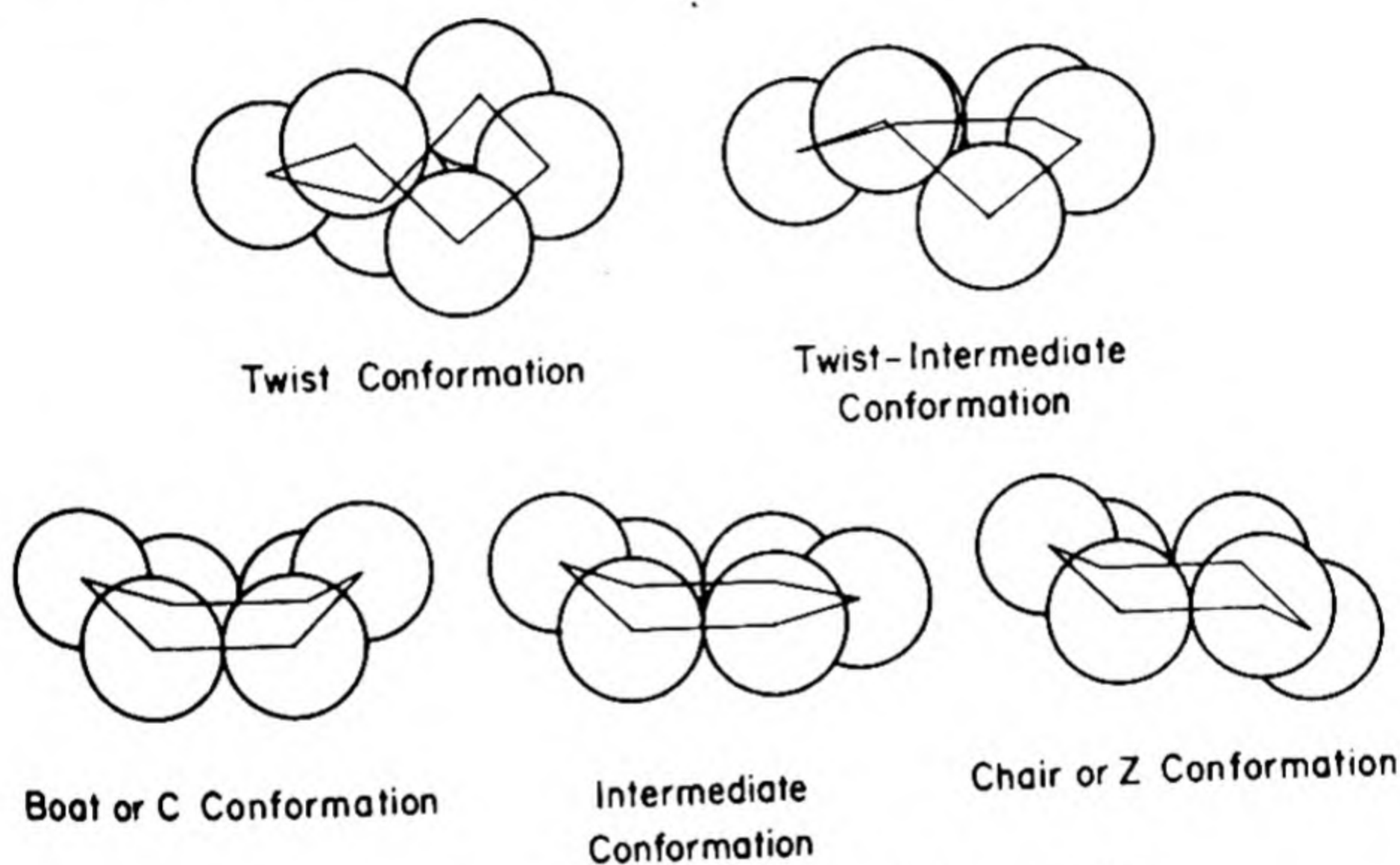


Fig. 5-5. Conformations of the Cyclohexane Ring.

Cyclohexane can exist, a priori, in two conformations, called chair and boat (Fig. 5-5). The six boat conformations are less stable than the two chair conformations because of eclipsing and other nonbonded atom interactions absent in the latter. Four eclipsing interactions occur along the parallel sides ("gunwales"). In addition, the two hydrogen atoms in the "flagpole" and "bowsprit" positions, the ones bent toward each other at the ends of the boat, are quite close together and interact to produce about 2 kcal. of strain energy (Fig. 5-6). Thus, the boat form is about 6-7 kcal./mole less stable than the chair form. However, some of this strain can be relieved by slightly twisting the boat to form the twist or skew-boat conformation (Fig. 5-5). This relieves much of the "flagpole-

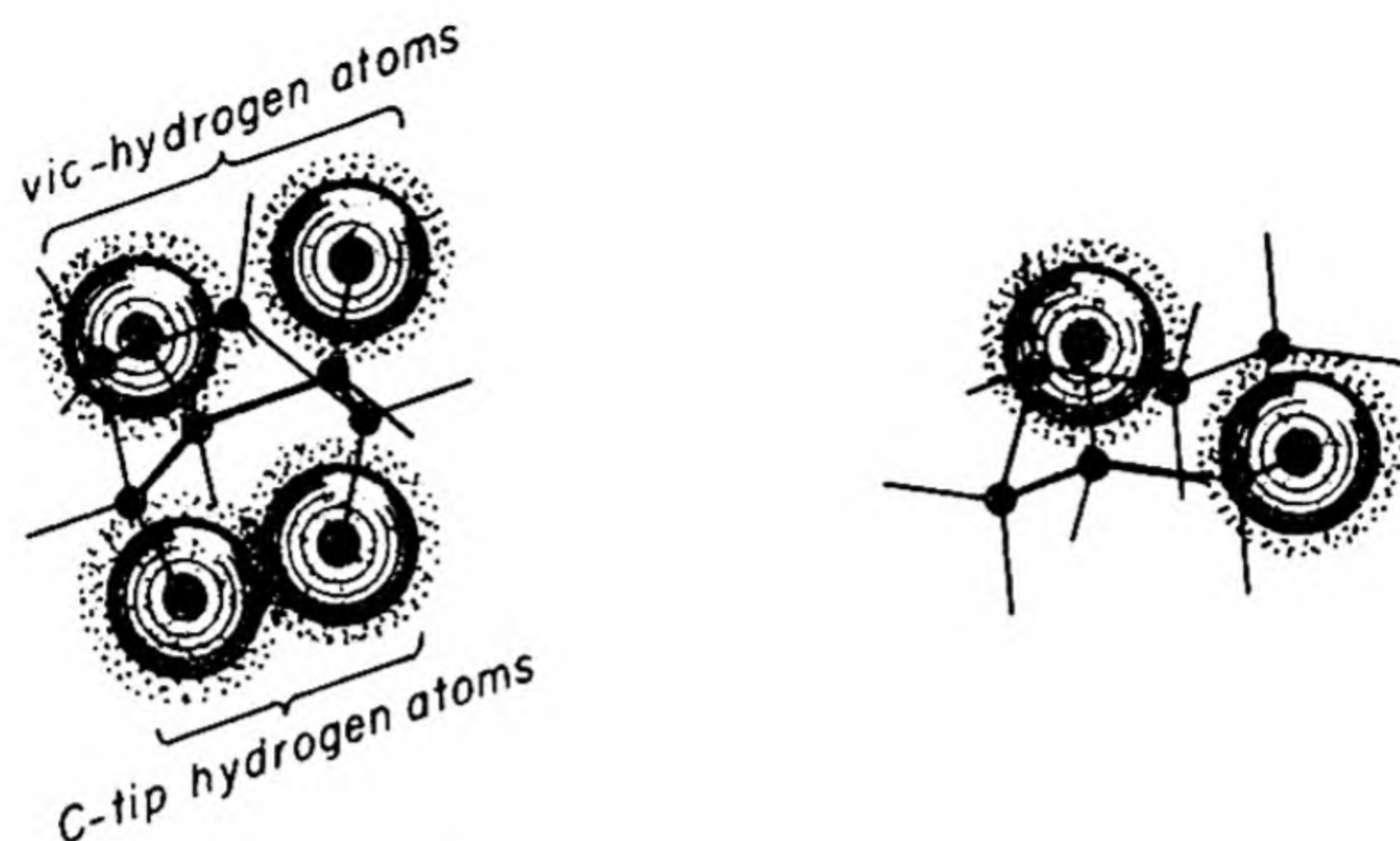


Fig. 5-6. Relative Repulsions between Hydrogen Atoms in Boat and Chair Conformations of Cyclohexane.

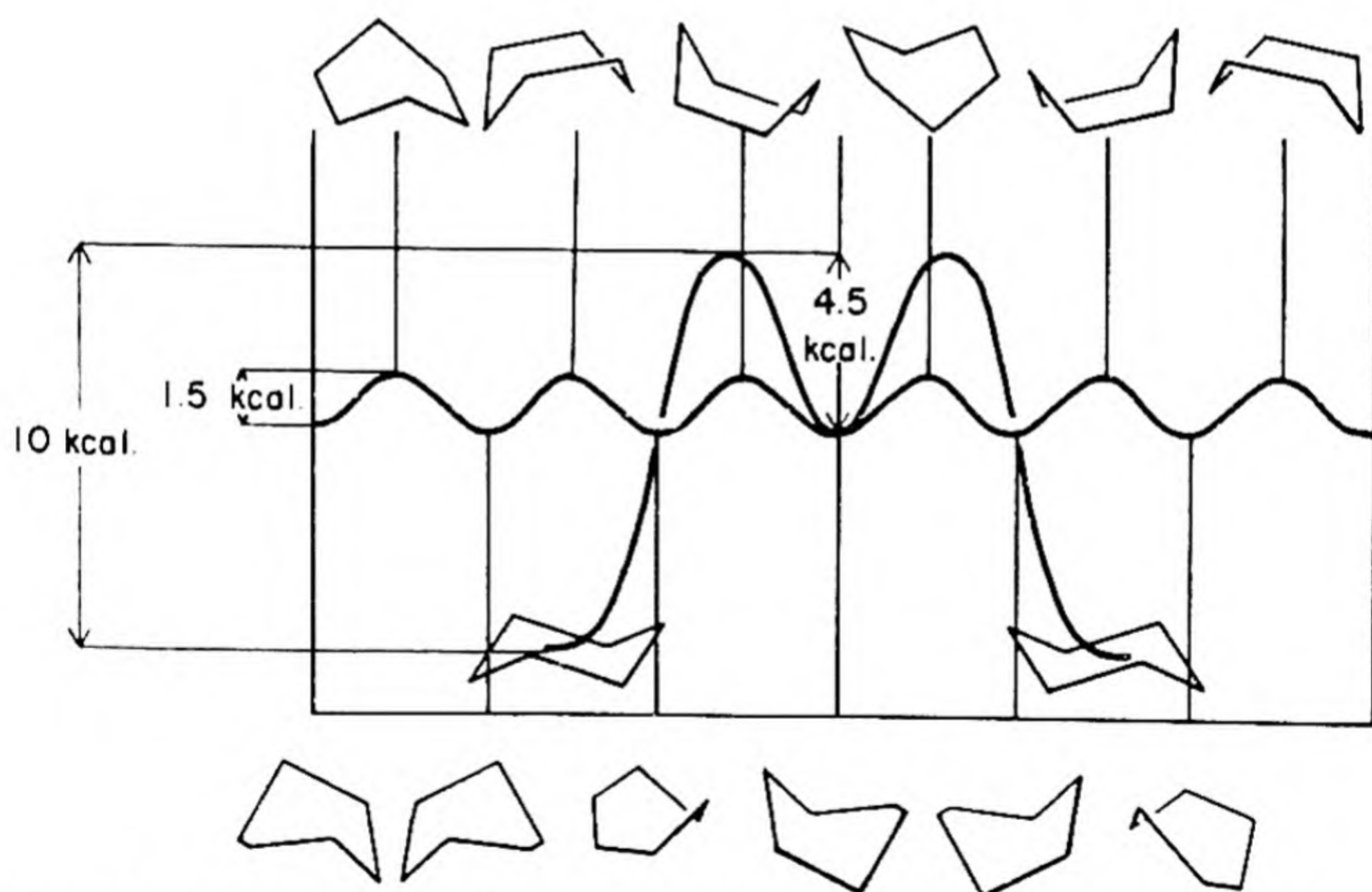


Fig. 5-7. Energy Diagram for the Interconversions of Cyclohexane. The wavy line with 1.5 kcal./mole amplitude represents the boat-twist flexing of the ring. The twin 10 kcal./mole curves represent interconversions between twist and chair conformations, with the twist-intermediate form at the crest of the curves. One pair of such curves occurs at each of the six twist conformation troughs. One curve of the pair leads to chair cyclohexane in which a particular hydrogen atom may be equatorial, the other to that in which the same hydrogen atom is axial.

bowsprit" interaction and some of the eclipsing strain, to the extent of about 1.5 kcal./mole. Furthermore, the twist conformation leads easily to the twist-intermediate conformation (Fig. 5-5) which is intermediate between the boat and chair conformations. This energy barrier is about 4.5 kcal. above the twist conformation and about 10 kcal. above the chair conformation (Fig. 5-7), so that passage in either direction is easy at 20°. However, the preference for the chair conformation over the twist conformation at 25° is 1000:1 in cyclohexane itself. Placement of groups other than hydrogen atoms on the ring affects the equilibrium point, but, in the absence of strong forces to the contrary, the predominant form of any cyclohexane ring is the chair form.

In the chair conformation, the six parallel groups which point up and down from the general plane of the ring (a in Fig. 5-8) are called axial groups. The six around the periphery of the ring (e in Fig. 5-8) are called

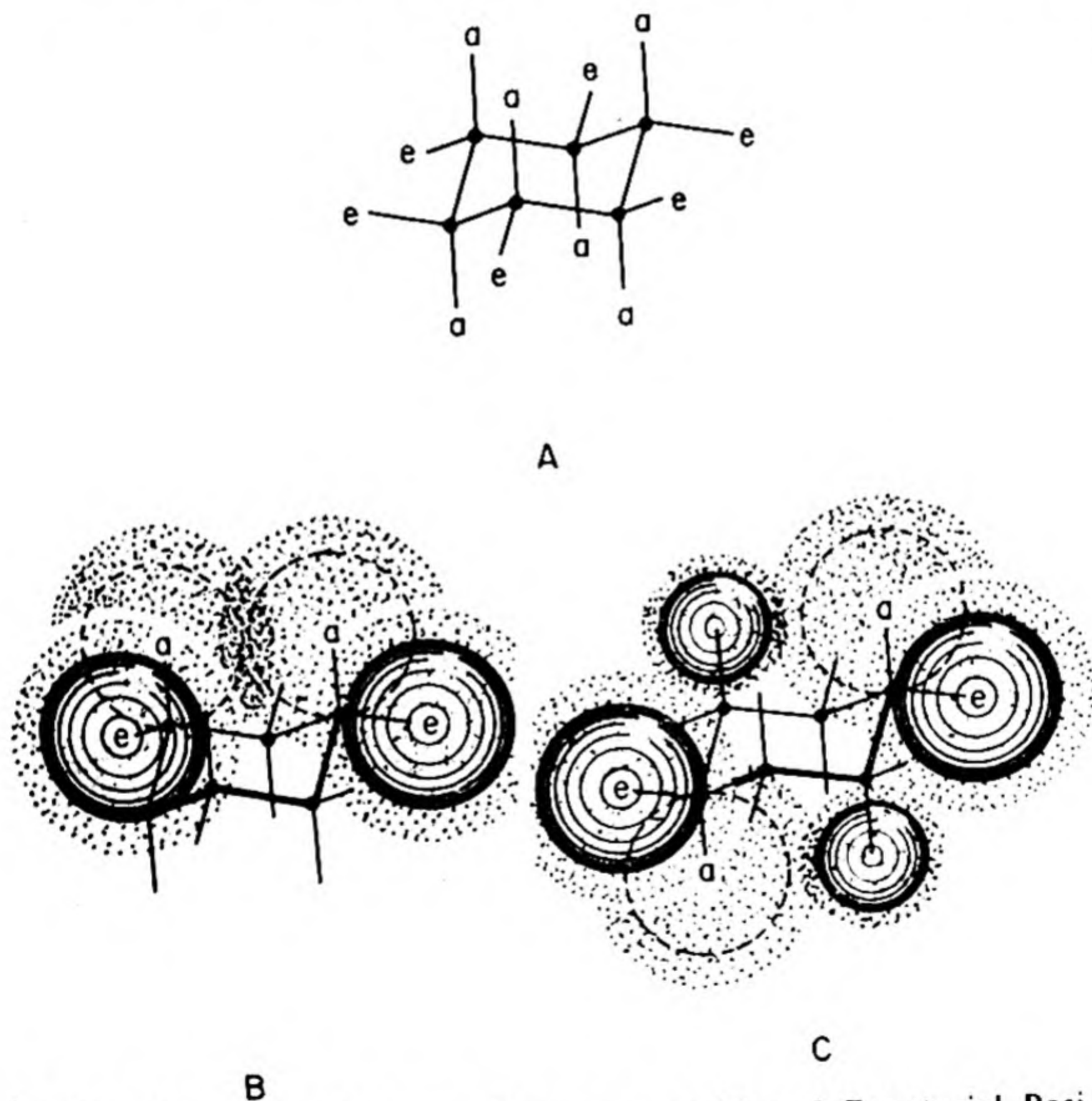
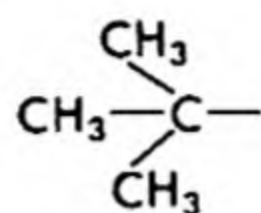


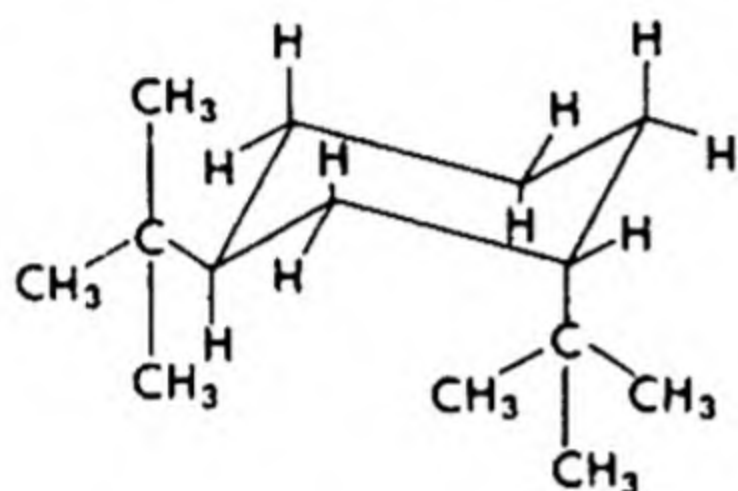
Fig. 5-8. Interference between Groups in Axial and Equatorial Positions. (A) Axial and Equatorial Positions, (B) Conformations of 1,3-*cis* groups (solid balls in preferred positions), (C) Conformations of 1,4-*trans* groups (solid balls in preferred positions).

equatorial groups. Large groups adopt equatorial orientations, since in these positions strong 1,3 diaxial interactions are avoided. The *t*-butyl group especially avoids the axial position because of strong repulsions

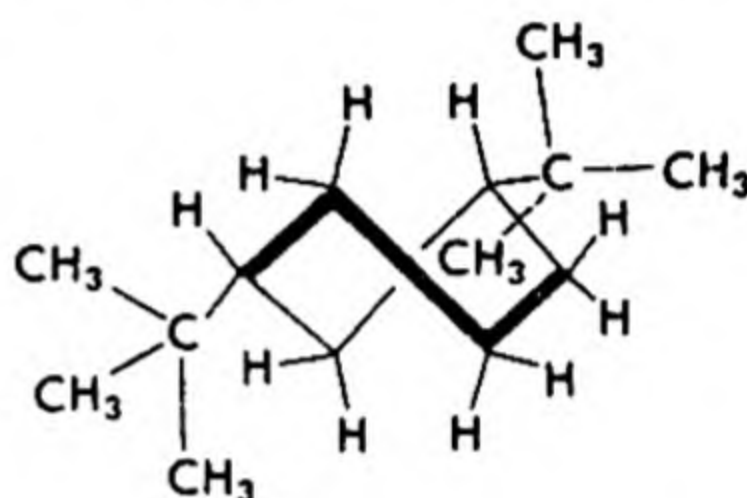


t-butyl group

toward the axial hydrogen atoms. Indeed, two *t*-butyl groups in appropriate positions can cause a cyclohexane ring to remain in the twist conformation. Such compounds of fixed conformation have been used as



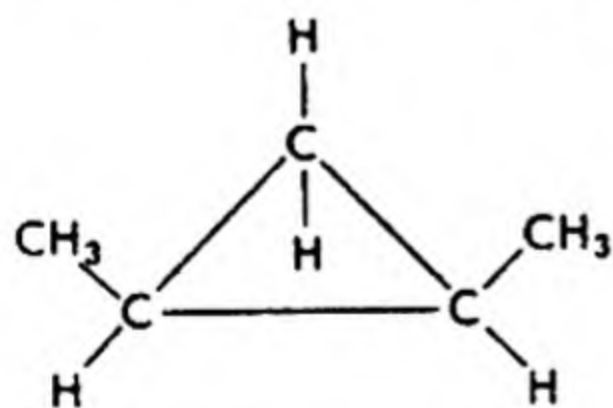
chair *trans*-1,3-di-*t*-butylcyclohexane,
with one *t*-butyl group in forbidden axial position



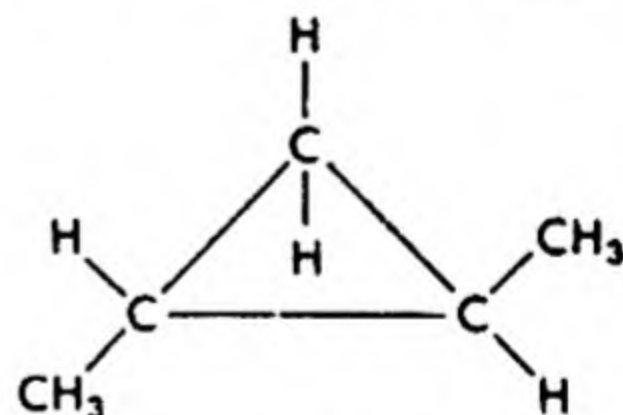
twist *trans*-1,3-di-*t*-butylcyclohexane,
with both *t*-butyl groups away from interfering
hydrogen atoms

models to determine the energy differences previously discussed for the forms of cyclohexane.

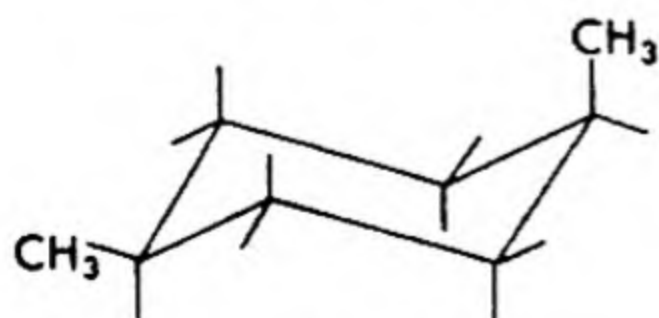
The π orbital of a double bond was seen (§5-1C) as one molecular feature which restricts rotation and thus makes possible geometric isomers. A closed chain (ring) effects the same result. Some examples of cyclic *cis-trans* isomers are given below. It should be apparent that



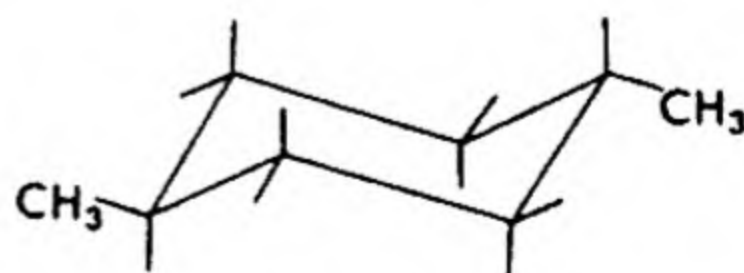
cis-1,2-dimethylcyclopropane



trans-1,2-dimethylcyclopropane



cis-1,4-dimethylcyclohexane

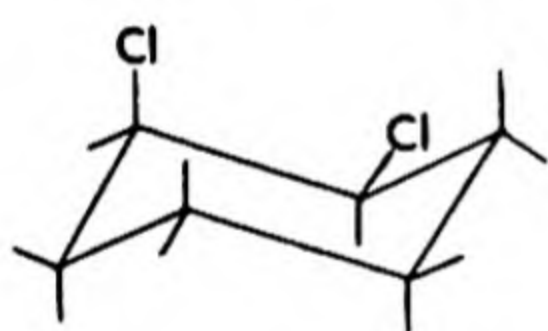
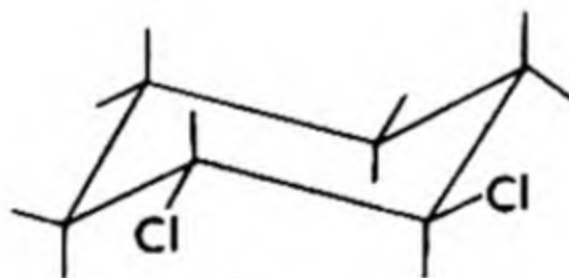
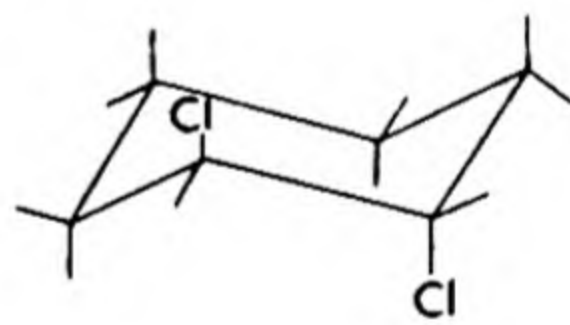


trans-1,4-dimethylcyclohexane

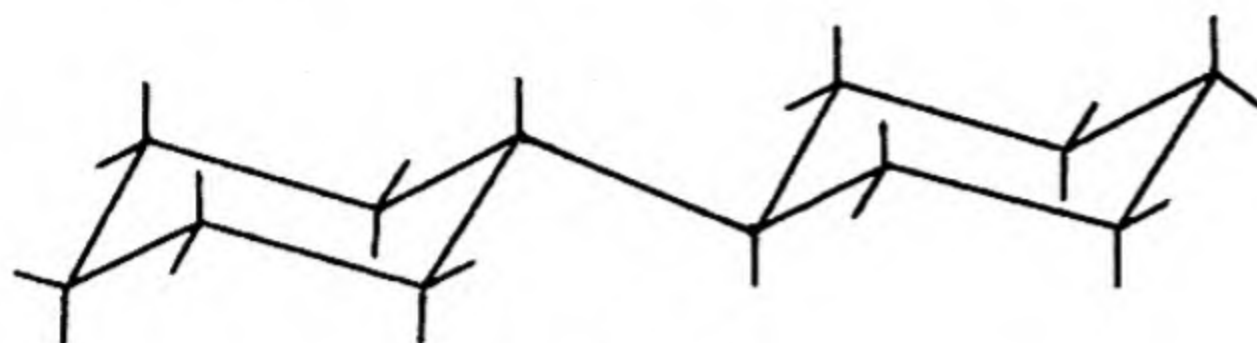
cis-1,2-dimethylcyclopropane cannot be converted into the *trans* isomer without rupturing the ring or exchanging one hydrogen atom and one methyl group, either of which involves high-energy processes in the pure hydrocarbon. (At least one C—H or C—C bond must be broken.) Conformation may obscure the relationships in cyclohexanes and larger rings. To avoid a complex discussion, all of the conformations of the 1,4-dimethylcyclohexanes may be considered to average out to planar representations as shown below. The *cis* and *trans* isomers are thus seen in their essential relationships to each other.

*cis*-1,4-dimethylcyclohexane*trans*-1,4-dimethylcyclohexane

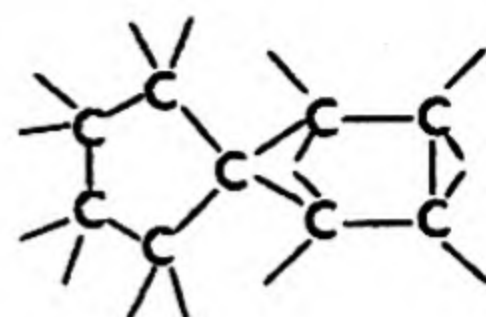
However, the student should spend some time with molecular models to become familiar with the intricacies of the actual conformations. For example, in *cis*-1,2-dichlorocyclohexane, one chlorine atom is equatorial, one axial. In *trans*-1,2-dichlorocyclohexane, both chlorine atoms are equatorial in one conformation, no farther apart than the atoms in the *cis* compound. The alternative conformation places both chlorine atoms in the *trans*-axial positions, where they are opposite to each other.

*cis*-1,2-dichlorocyclohexaneequatorial *trans*-
1,2-dichlorocyclohexaneaxial *trans*-
1,2-dichlorocyclohexane

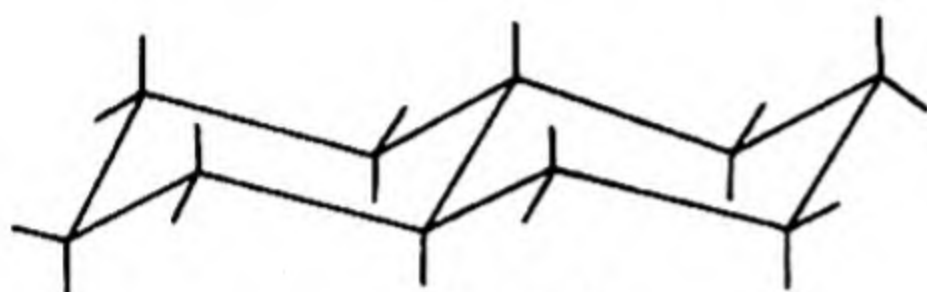
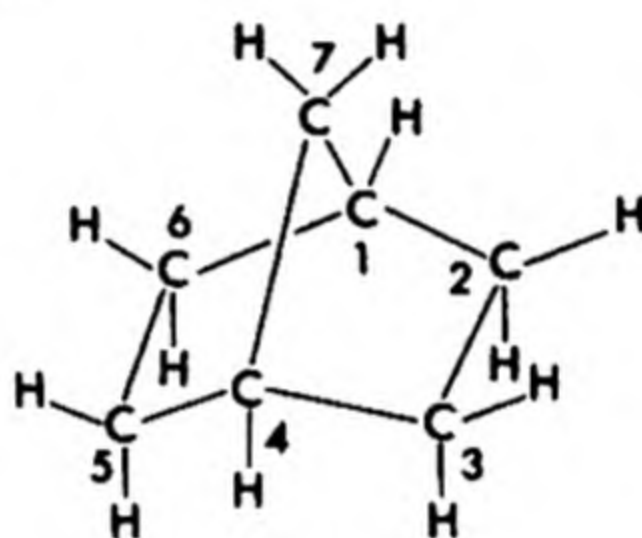
Systems with several rings connected in sundry ways are also common. The representative systems are those with *isolated* rings, such as bicyclohexyl; *spiro* systems, such as spirononane, in which *one* carbon atom is common to two rings; *fused* systems, such as the decalins, in which two atoms are common to two rings; and *bridged* systems, such as norbornane, in which more than two atoms are common to two rings.



bicyclohexyl



spirononane

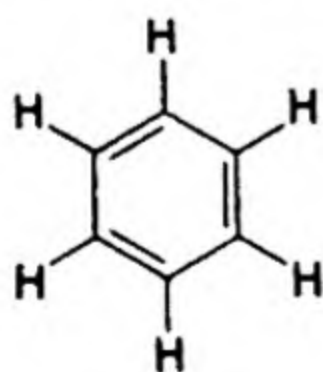
trans-decalin in
chair-chair conformationcis-decalin in one of the two
chair-chair conformations

norbornane

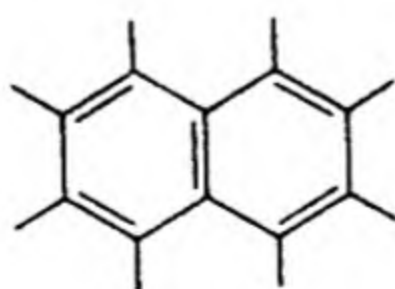
In a spiro system, the atom common to the two rings is called a spiro atom. In a bridged system, the carbon atoms which connect the rings, 1 and 4 in norbornane, are called *bridgehead* atoms. The groups of atoms which span between the bridgeheads are bridging groups, or *bridges*. Position 7 in norbornane is a methylene or methano bridge. Positions 2-3 or 5-6 in the same compound are ethano bridges.

When all of the atoms in a six-membered ring are trigonal (sp^2 hybridization), the ring is planar. Planar polycyclic systems can be built up like hexagonal tile mosaics.

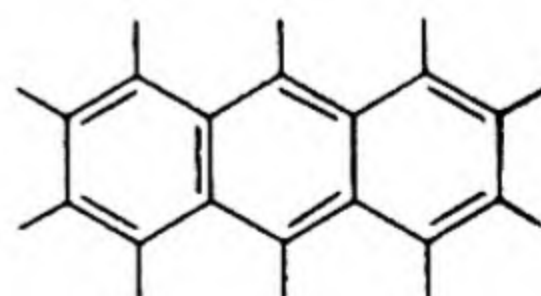
Some simple and complex aromatic systems are benzene, naphthalene, anthracene, and coronene. These ring systems are unsaturated; thus



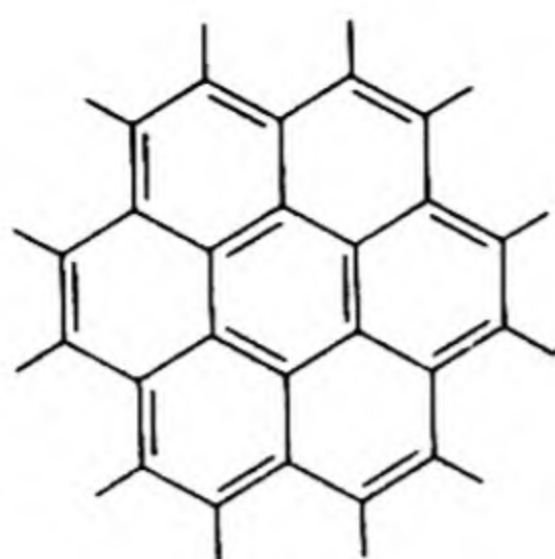
benzene



naphthalene



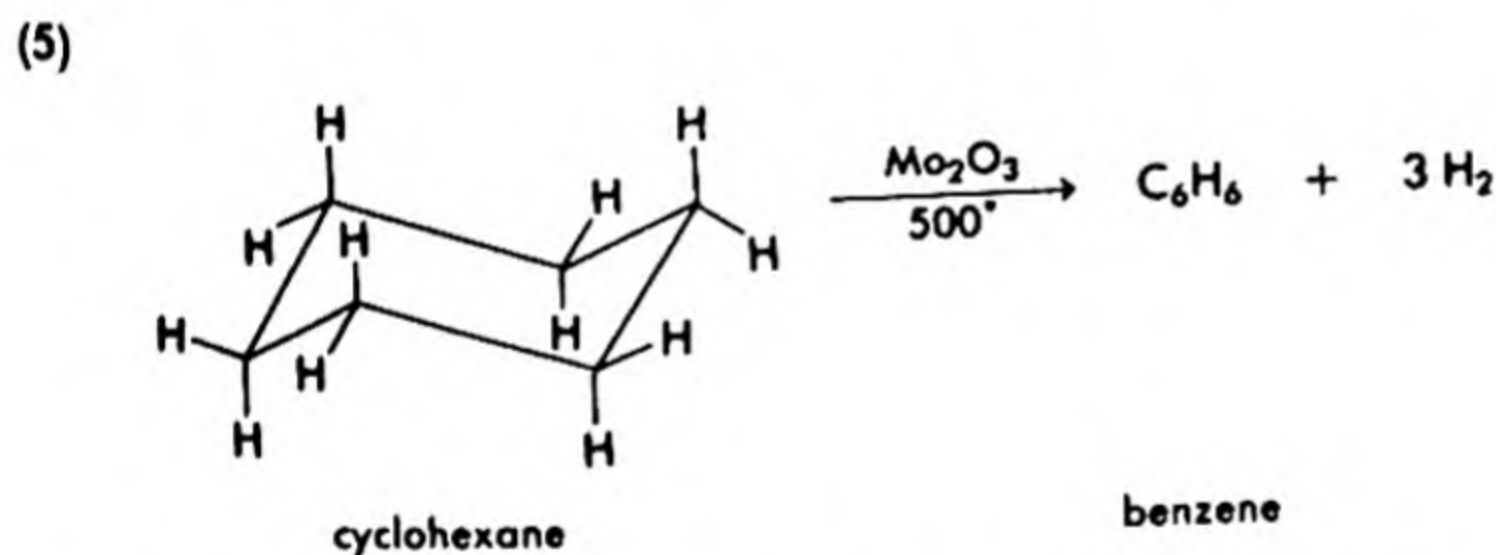
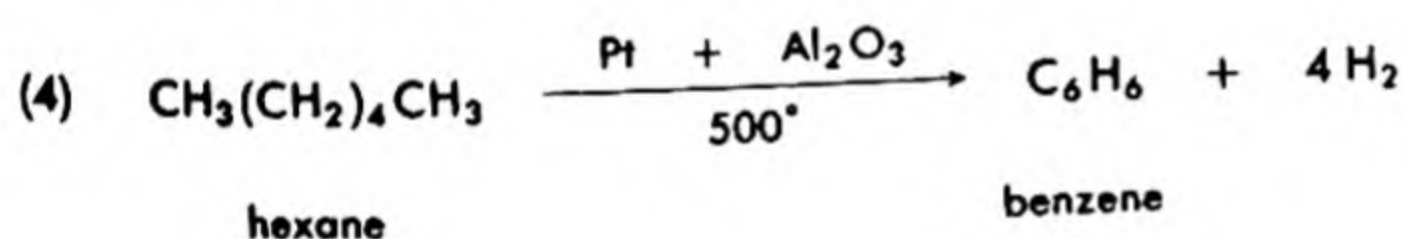
anthracene



coronene

formally they have double bonds. However, in these systems a special problem occurs regarding the placement and, in fact, the actual existence of the double bonds, which is discussed in the chapter on structure (§8-2G).

Hydrocarbons with aromatic rings are called *arenes*. A few (such as benzene and toluene) are found to some extent in certain petroleum, and some (benzene and naphthalene) in coal tar, but large quantities must be manufactured from petroleum fractions by *reforming*. In this process, alkanes and cycloalkanes are converted to arenes.

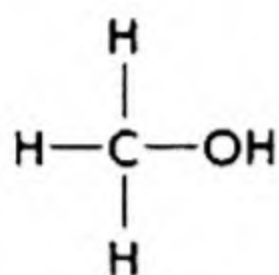


Cycloalkanes, cycloalkenes, and other compounds with nonaromatic carbocyclic rings are classified as *alicyclic* (contraction of aliphatic cyclic).

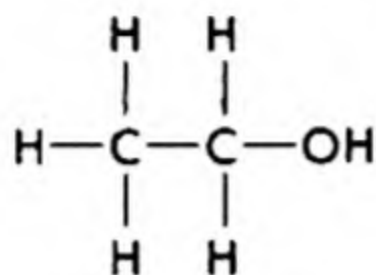
5-2 FUNCTIONAL GROUPS AND CLASSIFICATION OF COMPOUNDS

Those compounds which contain only hydrogen atoms on their carbon skeletons have been called *hydrocarbons*. The presence of other atoms entails different properties, hence a different classification of compounds. These *derivatives* of hydrocarbons, that is, compounds in which one or more hydrogen atoms of the hydrocarbon have been replaced by atoms of oxygen, nitrogen, halogens, or any others besides carbon, can be said to

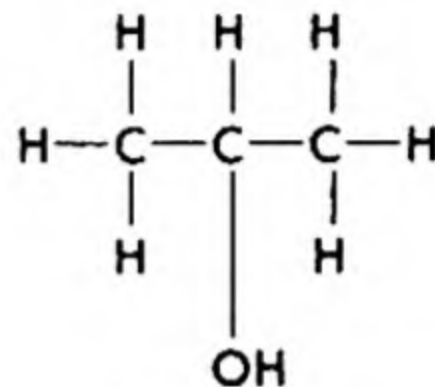
have two parts. These are the hydrocarbon group and a group made up of other kinds of atoms or multiple bonds called the *functional group*. This group functions to control the chemical properties of the compound in which it occurs. Thus, in the alcohols, the hydroxy (OH) group is the functional group, the remainder of the molecule the hydrocarbon group.



methanol
methyl group +
hydroxy group



ethanol
ethyl group +
hydroxy group

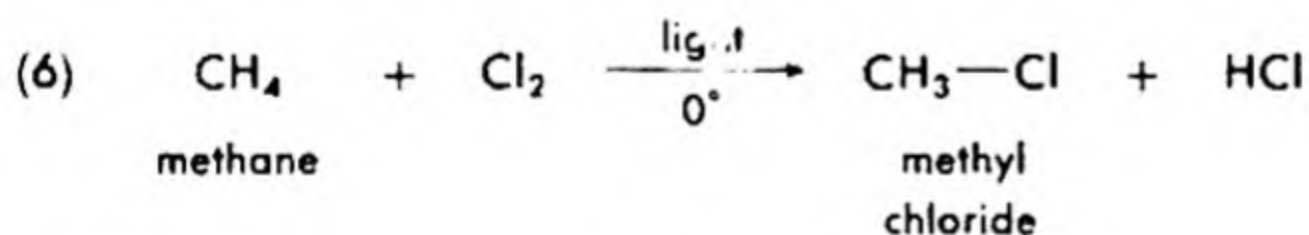


2-propanol
(isopropyl alcohol)
isopropyl group +
hydroxy group

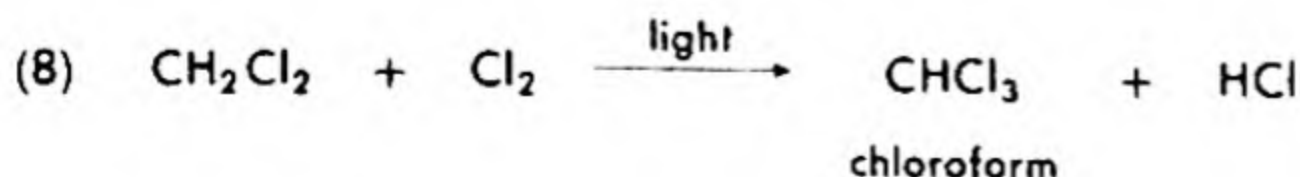
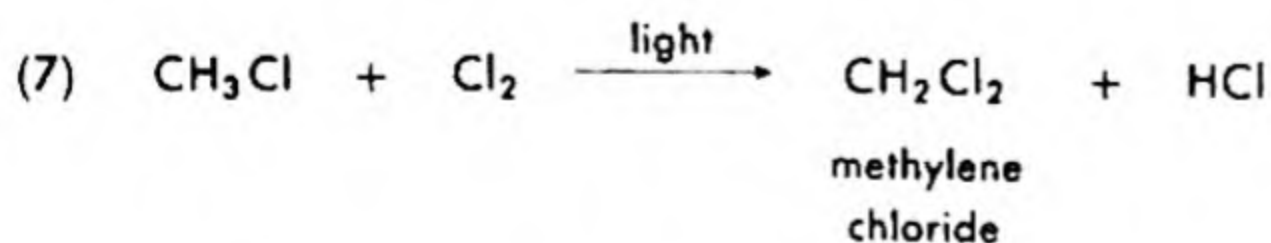
As was indicated (§5-1A), homologs have similar chemical properties. This is due to the fact that most of the chemical reactions occur at the functional group, not the hydrocarbon group. Those reactions that do involve the hydrocarbon group are usually strongly influenced by the functional group. For many of the chemical reactions of a series of homologs, one may ignore the nature of the hydrocarbon groups and concentrate on the nature of the functional group. For this purpose, the letter R is used to represent the hydrocarbon group. Thus, a generalized formula for alcohols is ROH. For some purposes, one must specify the structure in greater detail, as will appear in later examples.

A. Halides

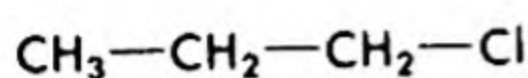
Replacement of a hydrogen atom in an alkane by a halogen atom forms an alkyl halide. This is practicable, as shown in eq. (6).



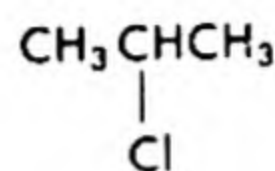
The *halogenation* shown in eq. (6) tends to continue so as to form polyhalides to some extent.



On a three-carbon chain a chlorine atom can assume either an end position or a central position. The isomeric propyl chlorides are thus *positional* isomers.

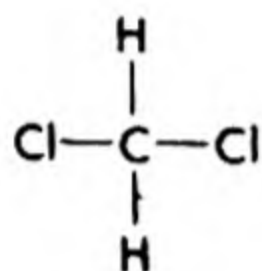


n-propyl chloride
1-chloropropane

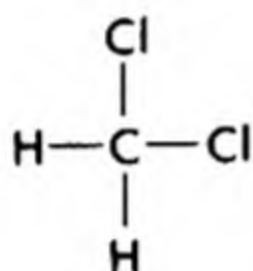


isopropyl chloride
2-chloropropane

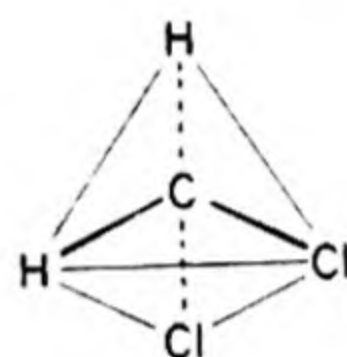
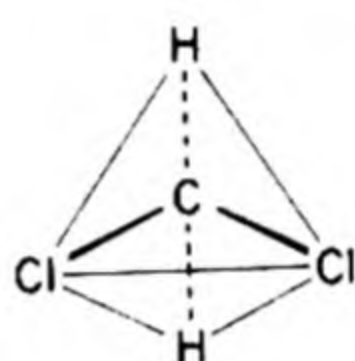
The absence of geometric isomerism in methylene chloride is of historical interest. If bonds on the carbon atom were planar or pyramidal, two isomeric methylene chlorides would exist. In fact, however, both paper structures of methylene chloride represent a single, unique molecule. This



hypothetical *anti*-
methylene chloride

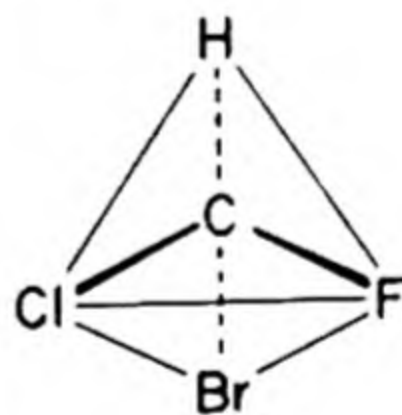
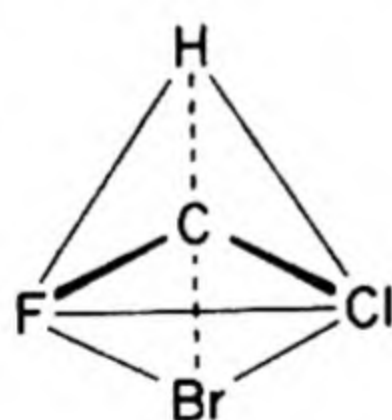


hypothetical *syn*-
methylene chloride



two orientations of actual
tetrahedral methylene chloride

is expected when the carbon atom is tetrahedral. Compounds such as fluorochlorobromomethane, which have four different groups about a carbon atom, exist as enantiomorphs (§5-1C).



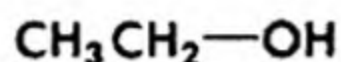
enantiomorphous trihalomethanes

Such right-handed and left-handed molecules could not exist if they were planar. Taken together, the existence of such enantiomorphs, angle strain, and several other bits of evidence point unmistakably to tetrahedral geometry for carbon atoms with a coordination number of four, as first proposed by van't Hoff (Utrecht) and LeBel (Paris) in 1874 (before angle strain was known).

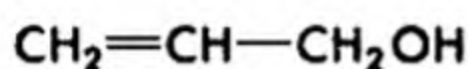
B. Oxy and Oxo Functions and Their Sulfur Analogs

Examples of compounds with the hydroxy function have been cited several times. The *alcohols* are compounds with one hydroxy group on a

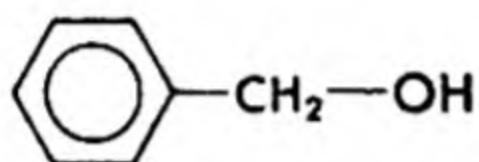
nonaromatic carbon atom. All homologs of methanol are alcohols, but not all alcohols are homologs of methanol, since unsaturated and cyclic hydrocarbon groups may be present. When the hydroxy group is on an aromatic ring, strikingly different chemical properties are observed, and the compounds are classified as *phenols*.

Alcohols

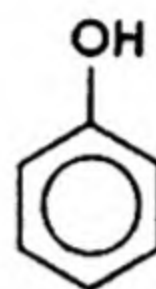
ethyl alcohol
(ethanol)



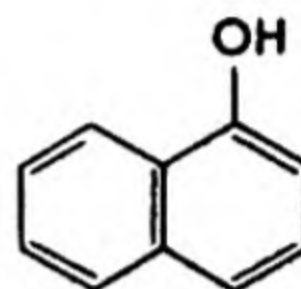
allyl alcohol



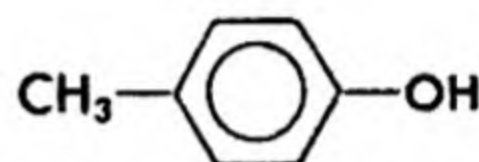
benzyl alcohol

Phenols

phenol



α -naphthol

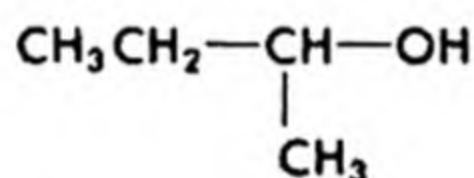


para-cresol (*p*-cresol)

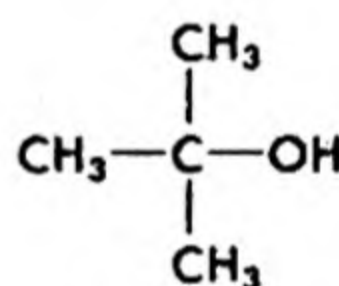
Alcohols are subclassified according to the type of alkyl group as primary, secondary, and tertiary alcohols.



n-butyl alcohol
(primary)



2°-butyl alcohol
(secondary)

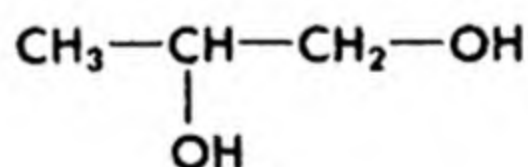


t-butyl alcohol
(tertiary)

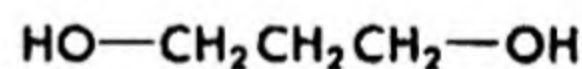
Alcohols with two hydroxy groups are called glycols.



glycol
(ethylene glycol)

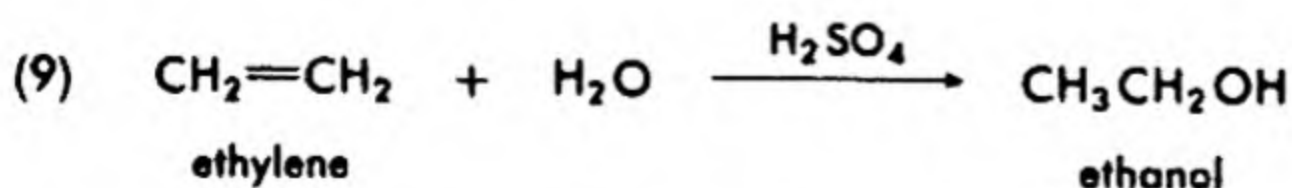


propylene glycol

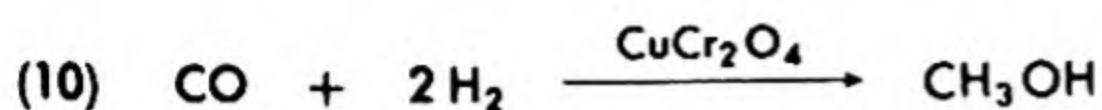


trimethylene glycol

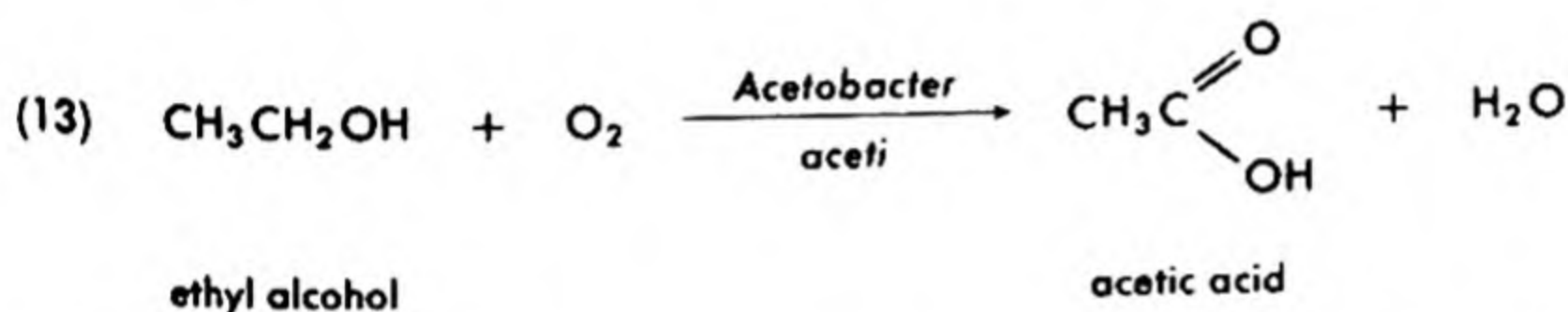
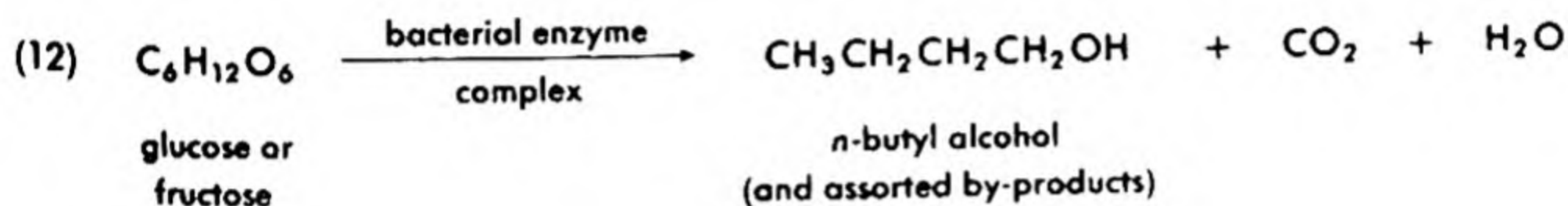
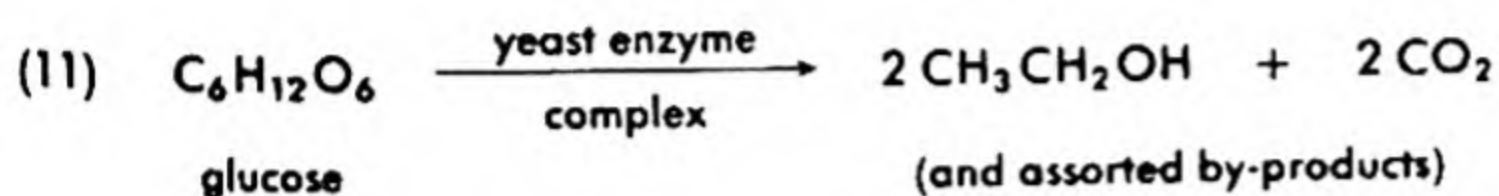
Alcohols and phenols are one oxidation step removed from hydrocarbons, but are not conveniently prepared by direct oxidation of hydrocarbons. One method of preparation of alcohols involves acid-catalyzed addition of water to an olefin.



Methanol is prepared industrially by catalytic reduction of carbon monoxide.

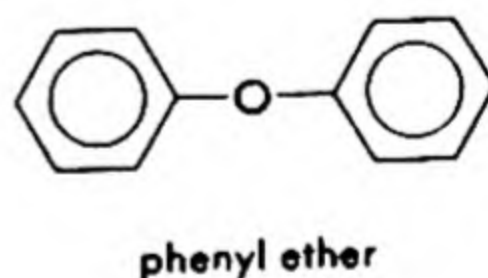
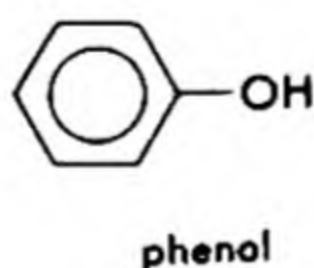
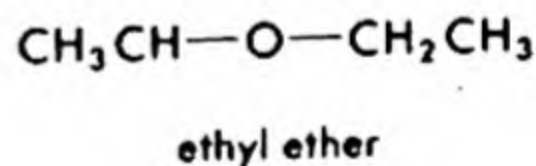
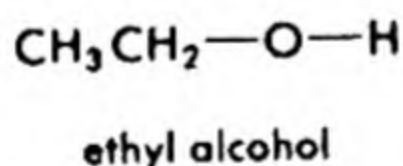
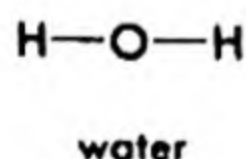


A very few alcohols (notably ethanol and *n*-butyl alcohol) are prepared by fermentation processes. One acid, acetic acid, is prepared for food use by bacterial oxidation of ethyl alcohol in air.

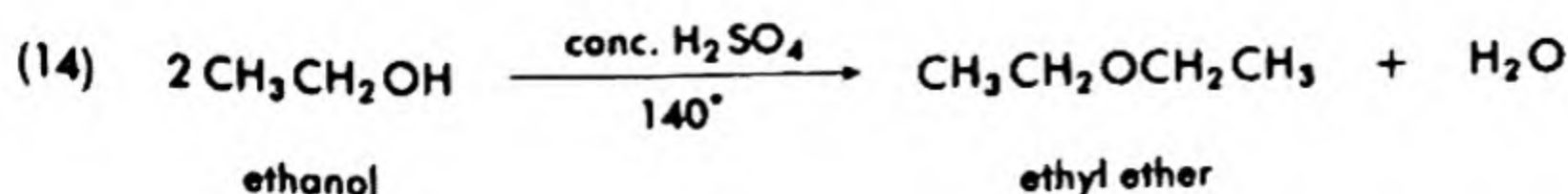


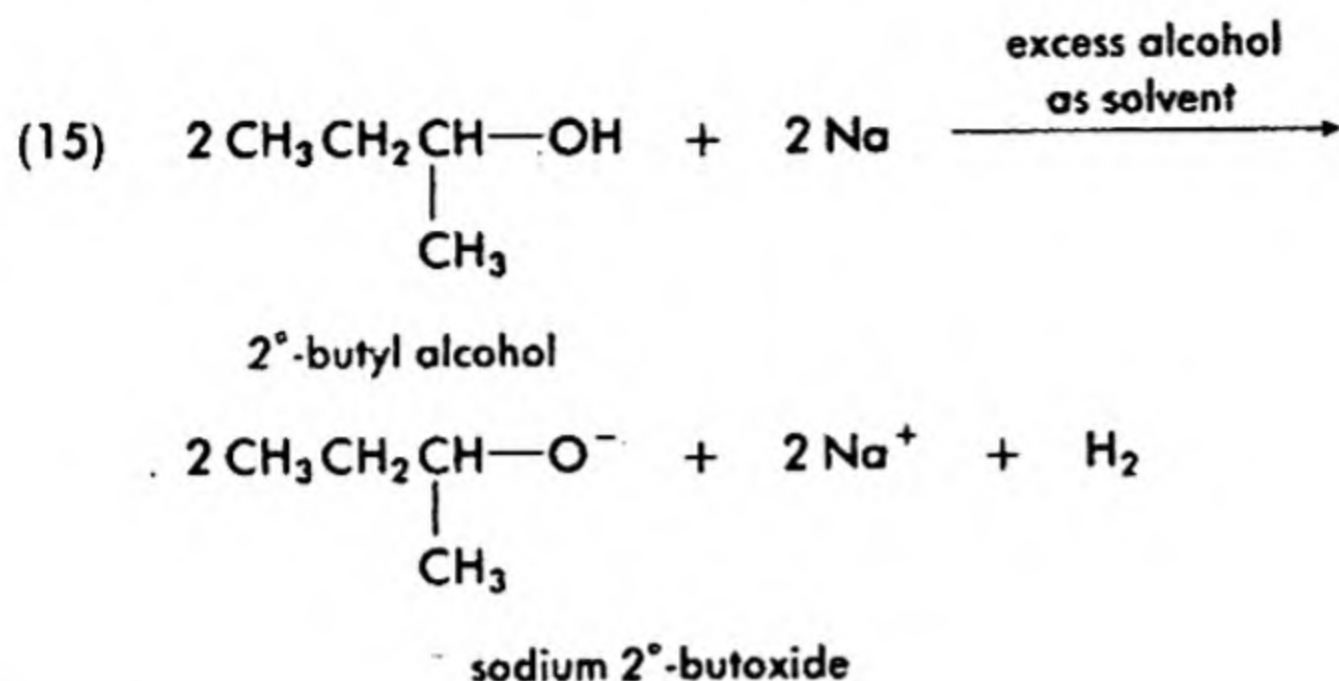
Phenols are prepared by more complex synthetic steps. Some, such as phenol itself and some of the cresols, can be isolated from coal tar. However, far larger quantities must be manufactured for their widespread uses as disinfectants and raw materials for phenolic resins and dyes.

Alcohols and phenols can be considered as derivatives of water with one hydrogen atom replaced by a hydrocarbon group. Replacement of the second hydrogen produces an ether.



Certain symmetrical aliphatic ethers can be produced by treatment of primary alcohols with hot sulfuric acid. Other methods are more suitable for most unsymmetrical ethers and ethers derived from alcohols other than primary.

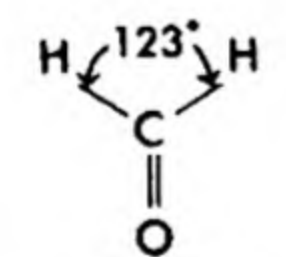




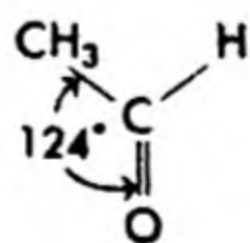
Ethyl ether is a widely used anesthetic.

Two hydroxy groups are not usually stable on the same carbon atom (recall carbonic acid). Instead, a dehydrated derivative, which contains the carbonyl group, an unsaturated carbon-oxygen group, is the product of a second stage of oxidation at one carbon atom. Two classes are recognized, $\text{H}-\underset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{H}$ and $\text{RCH}=\text{O}$, called aldehydes, and $\text{R}-\underset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{R}'$,

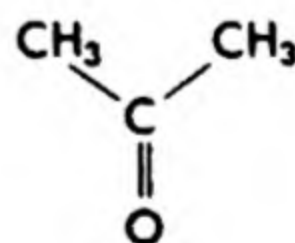
called ketones (when both R groups are hydrocarbon groups). Like the carbon-carbon double bond, the carbonyl group has a trigonal π orbital so that in an aldehyde or ketone the carbonyl group and the atoms attached directly to it are in the same plane with approximately 120° bond angles.



formaldehyde

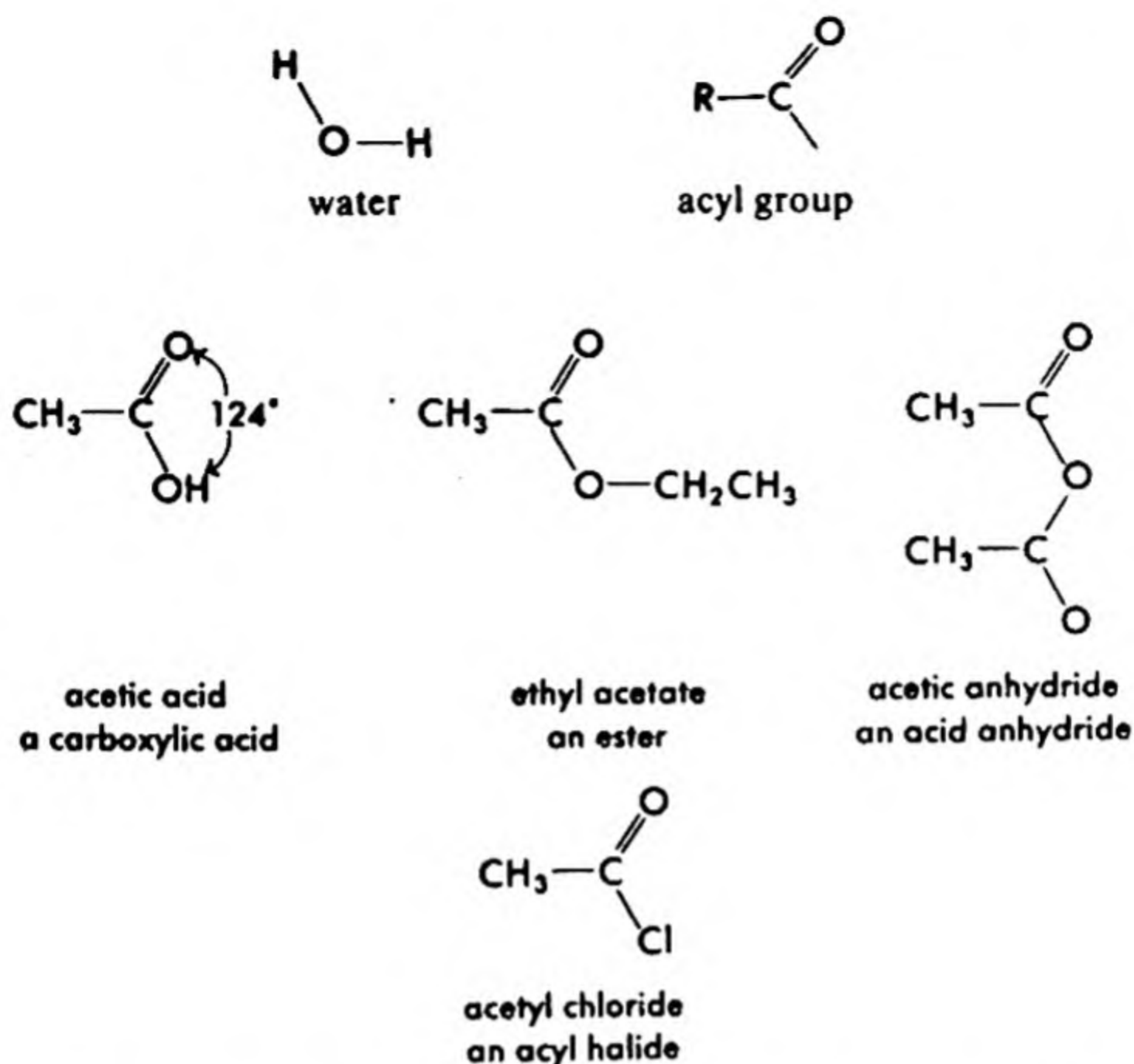


acetaldehyde

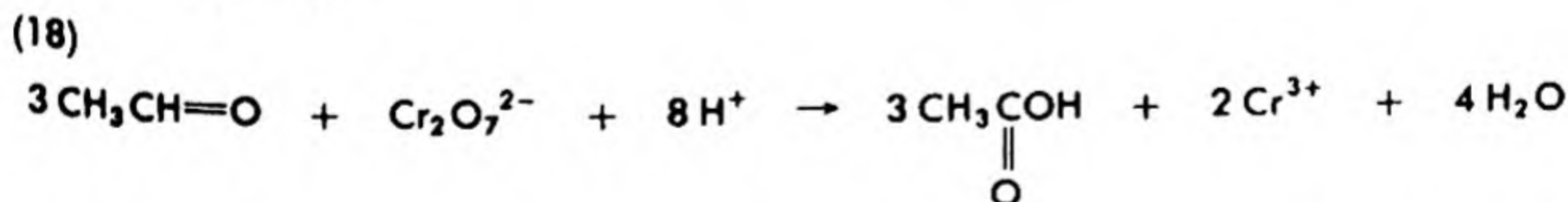
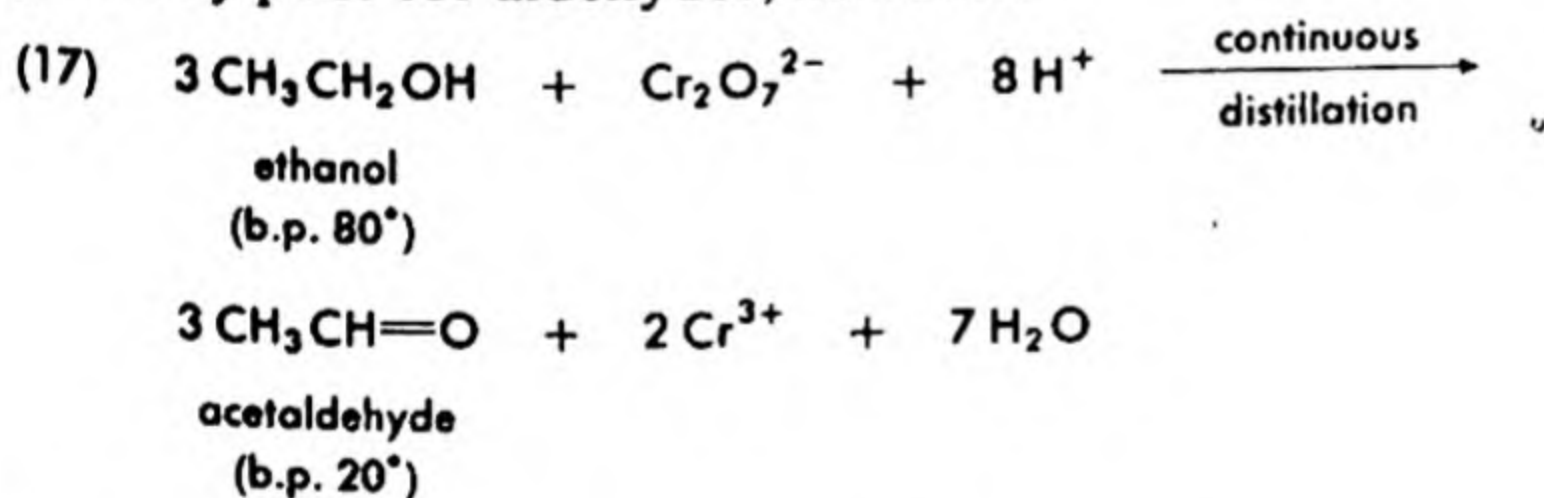


acetone

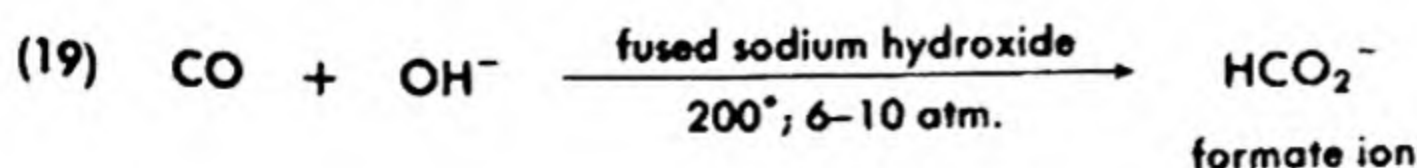
Several classes of compounds in addition to aldehydes and ketones contain the carbonyl group. Among these are carboxylic acids, which have a carboxyl group (*carbonyl* + *hydroxyl*), and their derivatives, the esters, anhydrides, and acyl halides. Carboxylic acids, esters, and anhydrides are *acyl* derivatives of water.

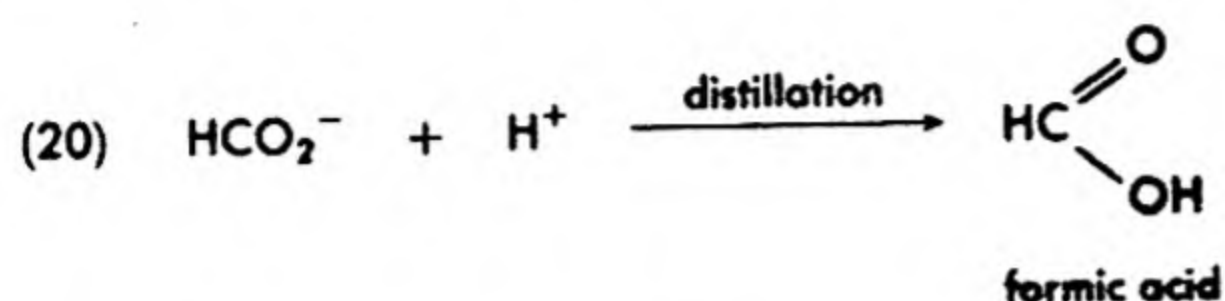


In the carboxyl and related groups, the carbon atom is at its third stage of oxidation, the highest stage possible for a carbon atom attached to another carbon atom. Aldehydes, ketones, and acids can, in fact, be prepared by oxidation of the next lower oxidation state; the method is generally poor for aldehydes, however.

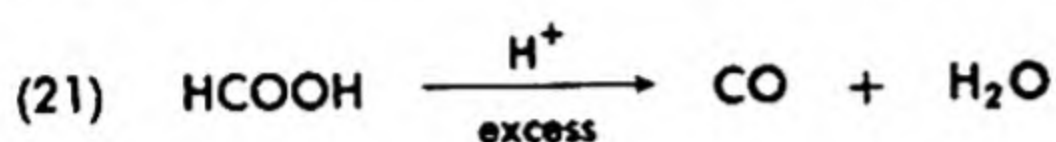


Formic acid is prepared industrially from carbon monoxide, although large quantities are now available as a by-product of pentaerythritol manufacture (§23-1A). The sodium formate produced in the first step (eq. 19) is neutralized by an exactly equivalent amount of sulfuric acid.

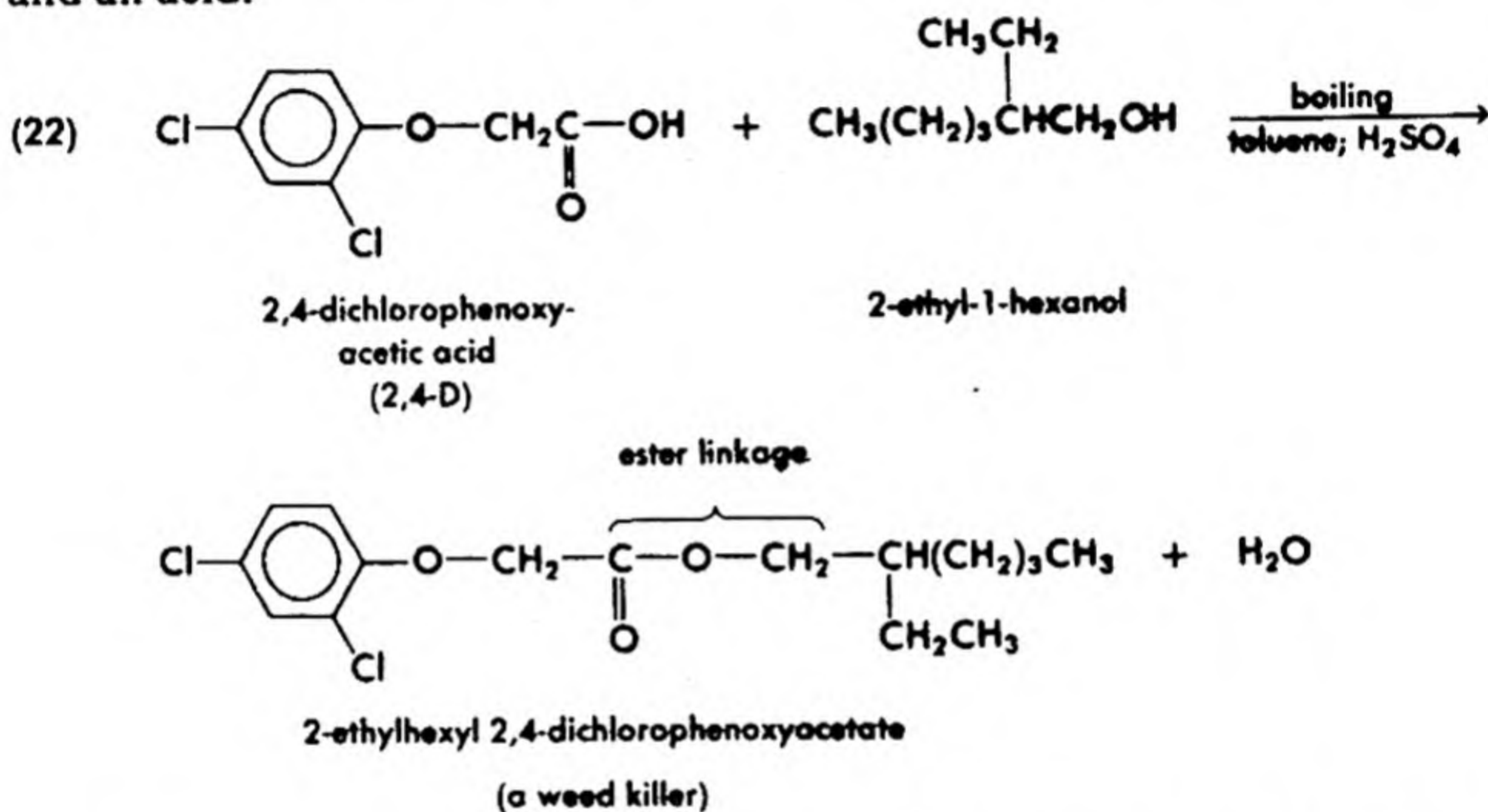




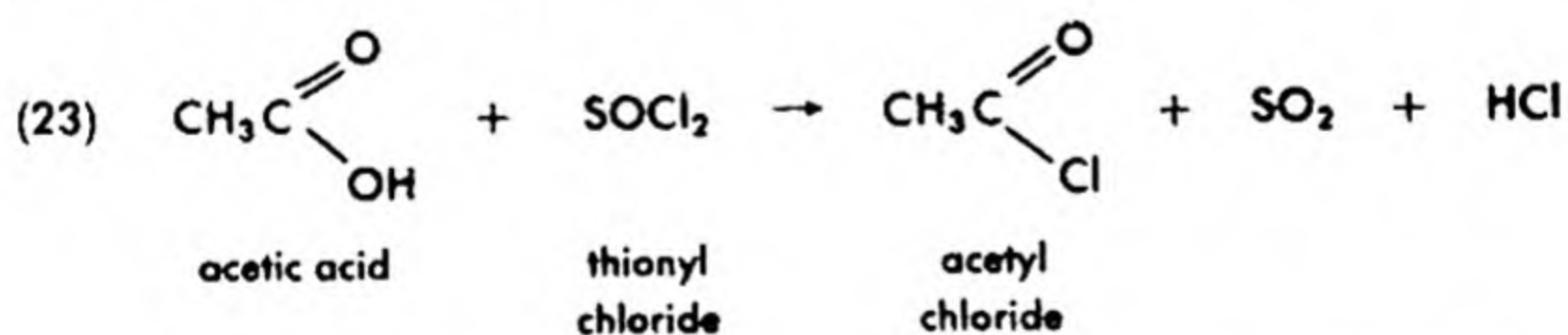
An excess of sulfuric acid decomposes formic acid.



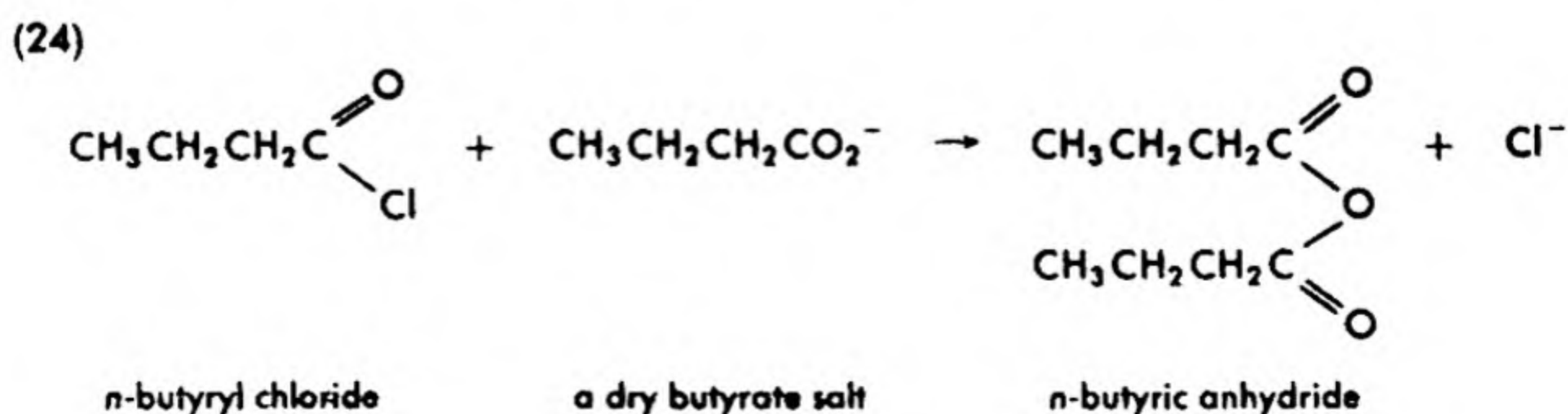
An ester can be produced by acid-catalyzed reaction between an alcohol and an acid.



An acyl halide is prepared from an acid and an inorganic nonmetal halide, such as thionyl chloride.

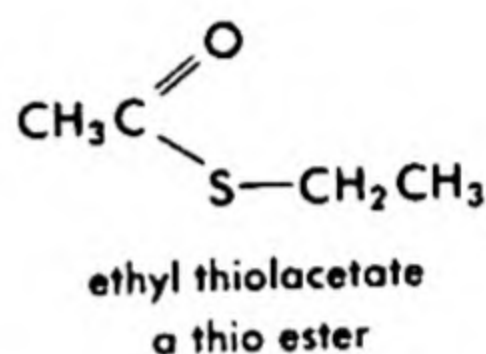
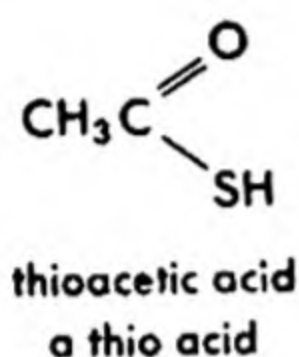
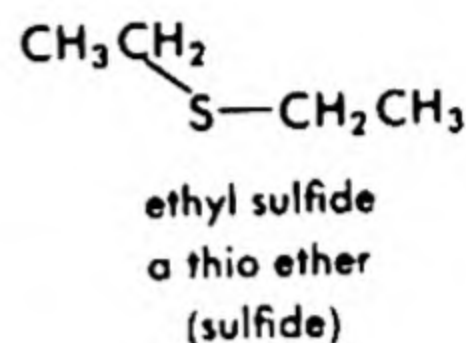
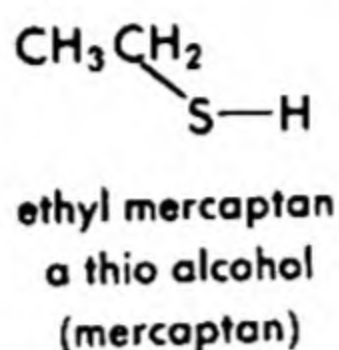
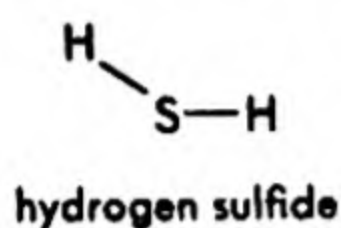


An anhydride can be prepared from an acyl chloride and the salt of an acid.

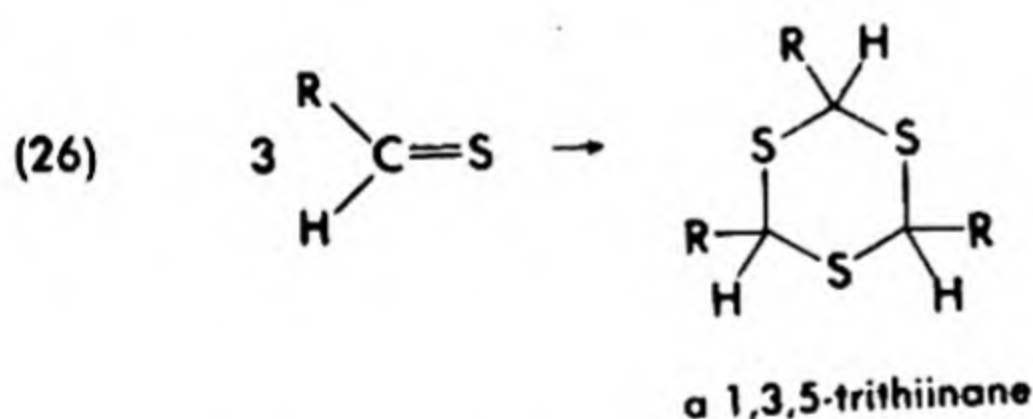
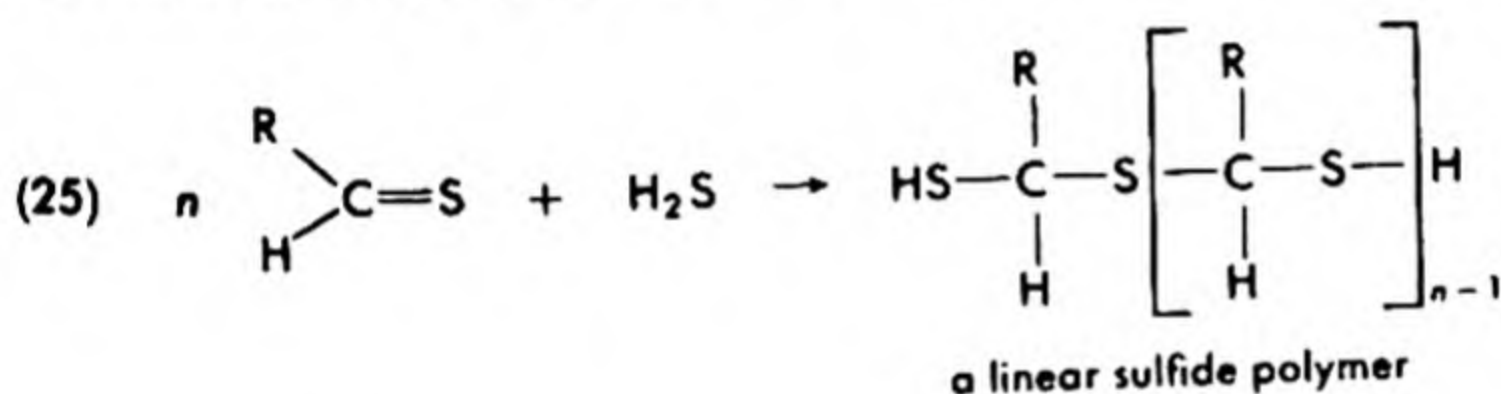


Many esters and ketones and some aldehydes are fragrant oils of value in perfumery and food flavoring.

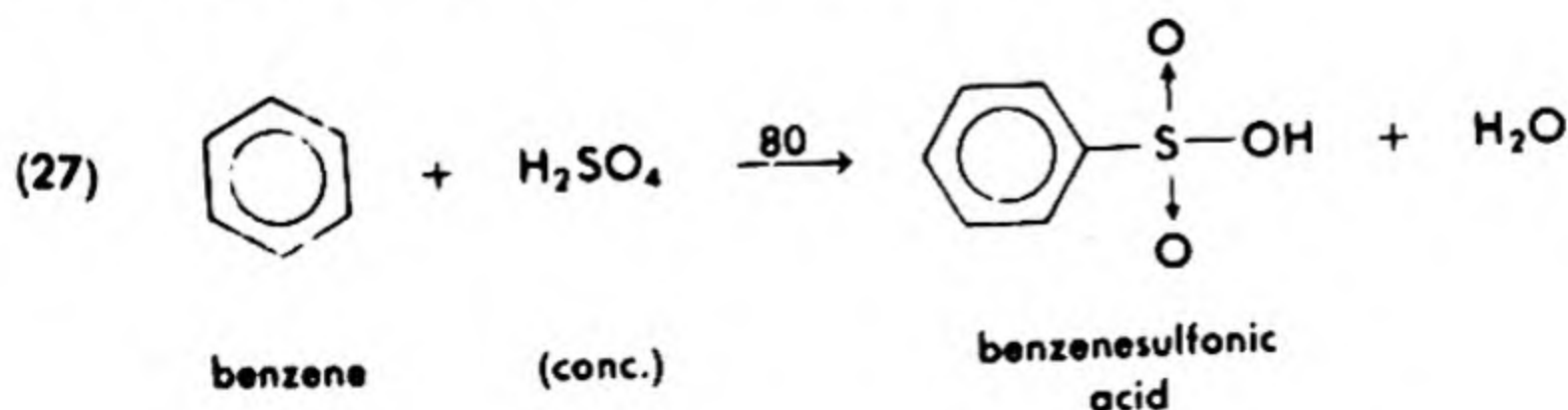
Alcohols, ethers, carboxylic acids, and acid derivatives are paralleled by sulfur analogs. These are related to hydrogen sulfide in the same manner that the oxygen compounds are related to water.



Thio analogs of aldehydes and ketones are uncommon, since these compounds tend to polymerize into linear or cyclic polymers.

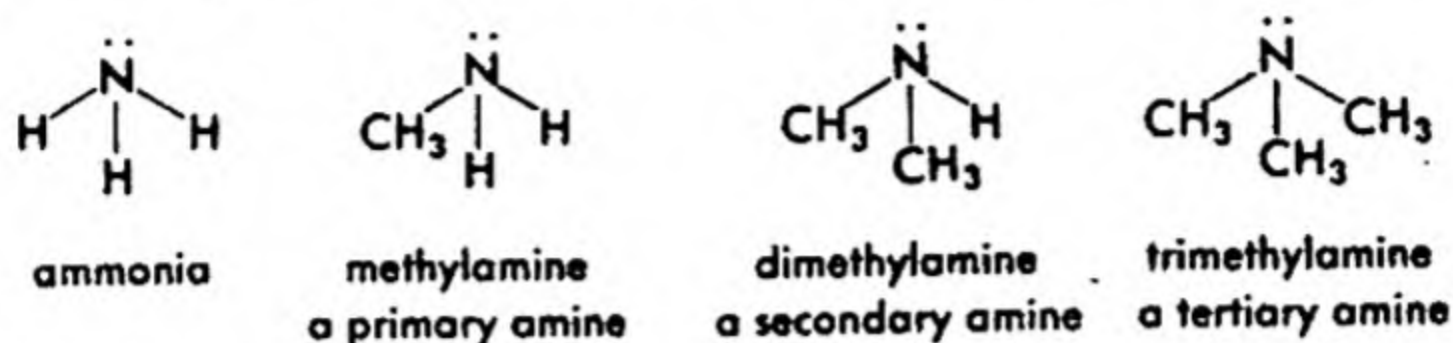


Some sulfur compounds have no oxygen analogs, due to differences in oxidizability of the two atoms. Sulfonic acids are an important class of this type. Aromatic sulfonic acids are formed by heating suitable hydrocarbons with concentrated sulfuric acid.



C. Nitrogenous Functions

Ammonia provides the basis for large numbers of important organic compounds. Alkyl and aryl derivatives of ammonia are *amines*.

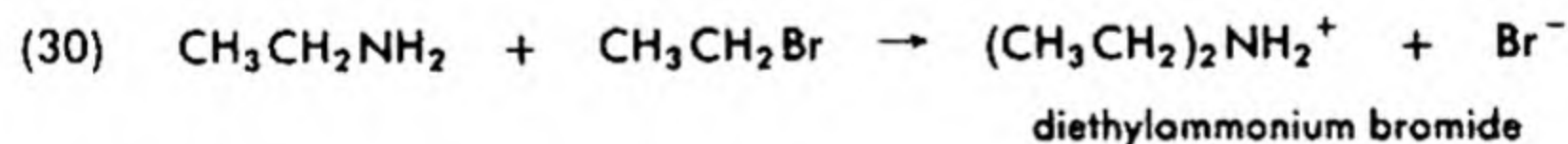
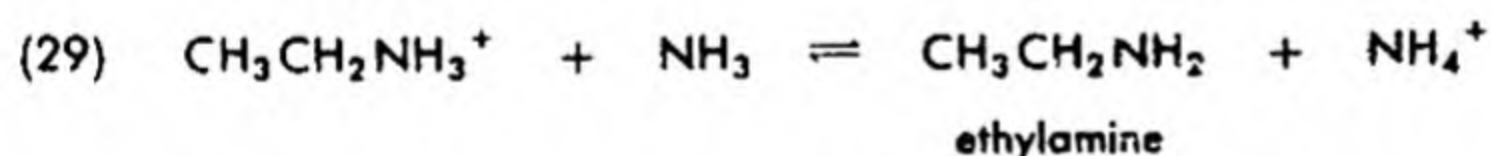
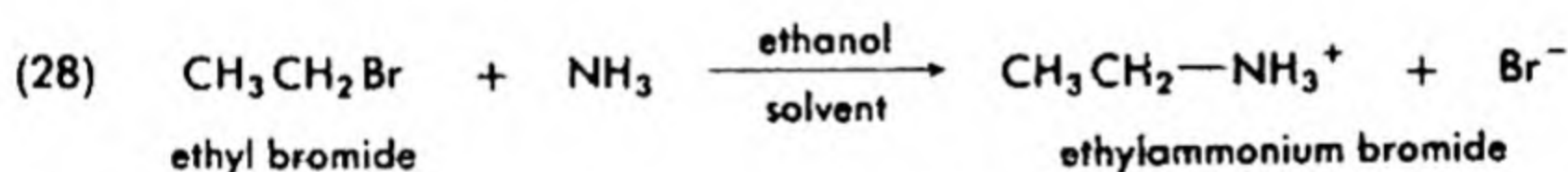


As is indicated in the formulas above, ammonia and amines have pyramidal bonds. When the unshared electron pair is included, the bonding and unshared pair orbitals are approximately tetrahedral.

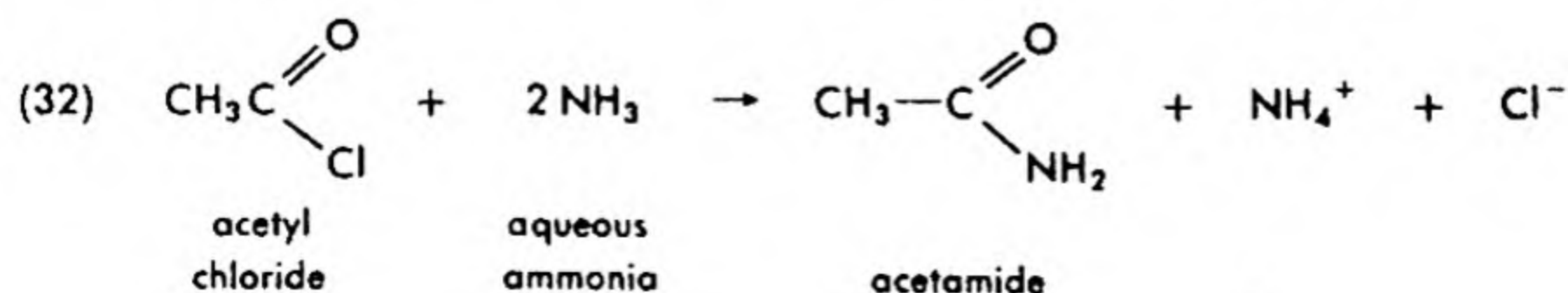
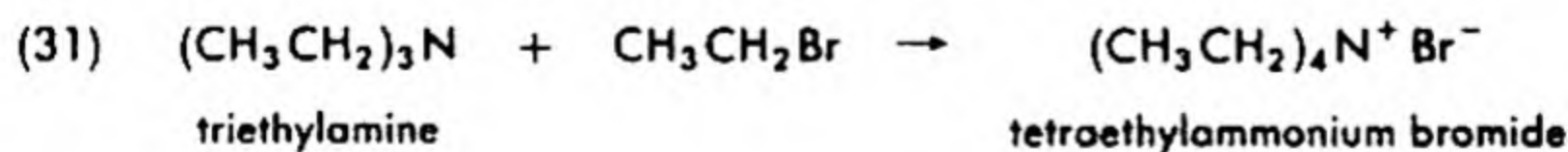
Acyl derivatives of ammonia are amides and imides. These resemble carboxylic acids and acid anhydrides, respectively, in spatial arrangement.



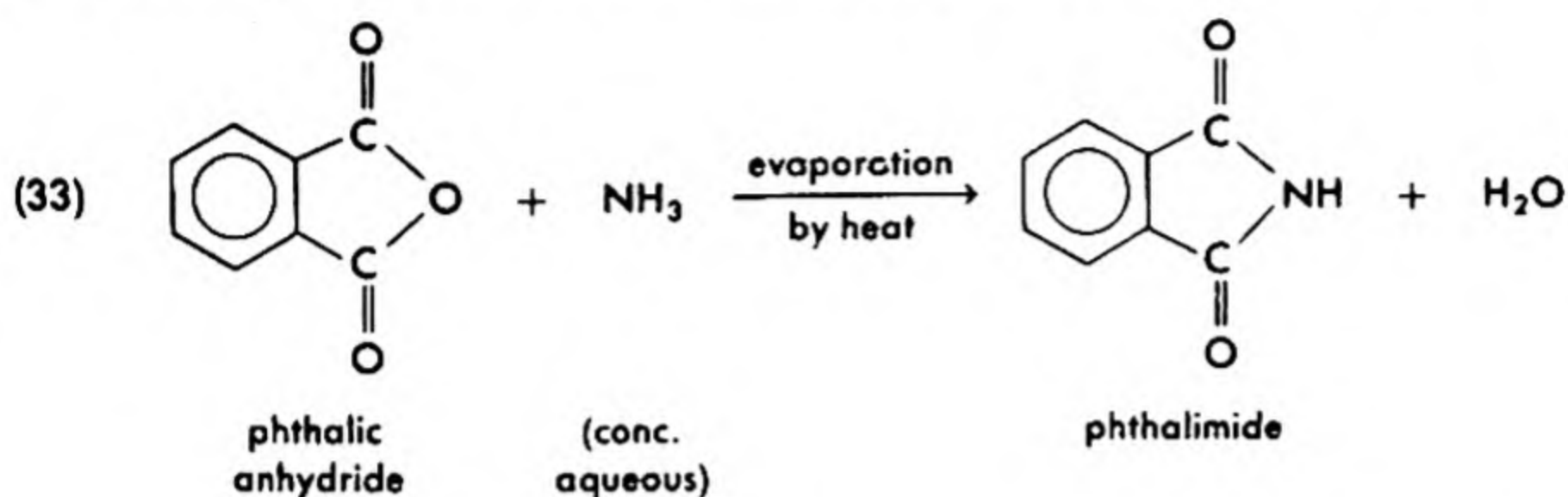
Amines and amides can be prepared by treatment of the appropriate halide with ammonia.



The reactions of this series continue with the production of secondary amines, tertiary amines, and finally, quaternary ammonium salts (which are not related to any amine by simple salt formation).

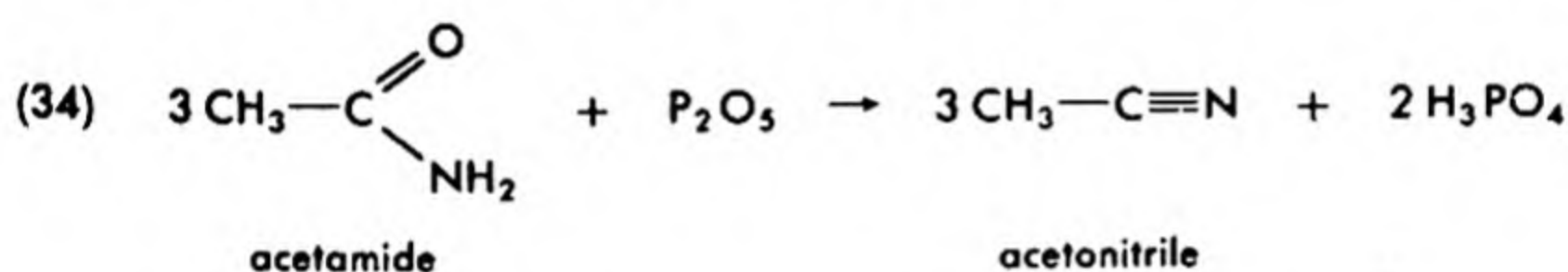


Cyclic imides, such as succinimide (above) and phthalimide, are readily prepared by treatment of the related anhydrides with ammonia.

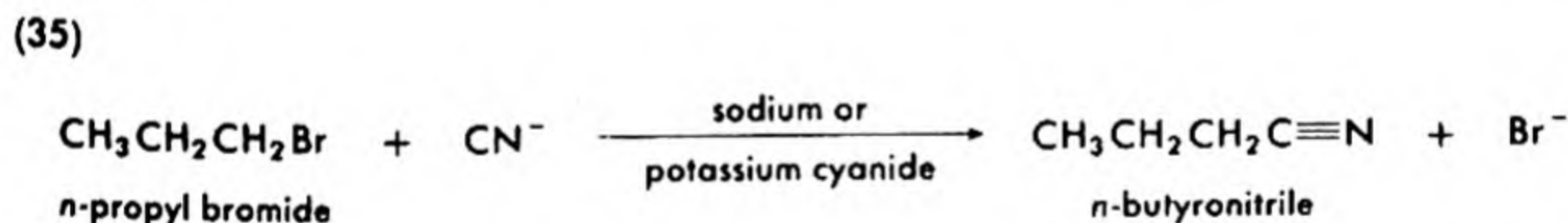


Imides which do not involve five- or six-membered ring formation are prepared with more difficulty. This is an example of the importance of geometry to chemical reactions.

If a simple amide is dehydrated by a suitable strong reagent, a nitrile, which has a carbon-nitrogen triple bond, results.

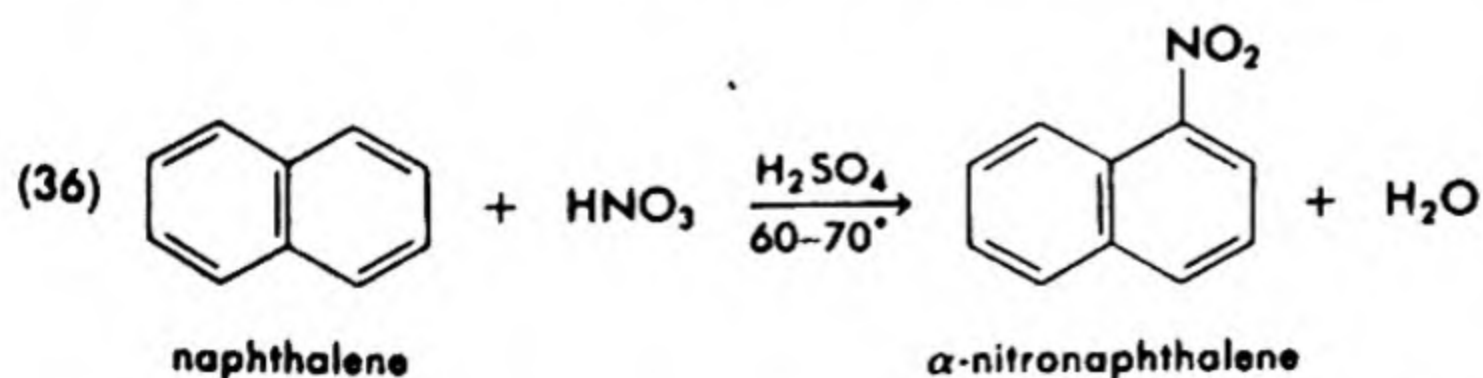


An alternative method for preparing a nitrile is displacement of halide by cyanide.

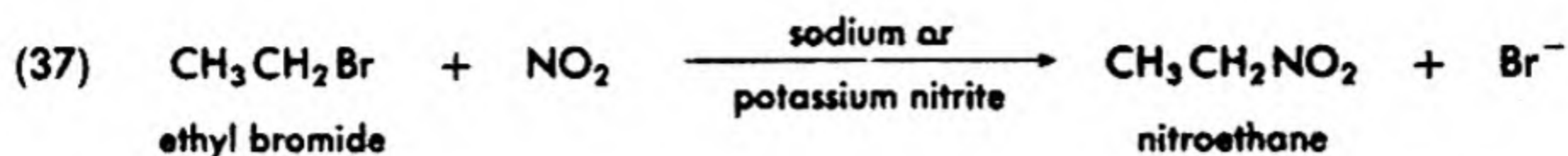


The carbon atom in the nitrile function, like that in an acetylene, is digonal (linear).

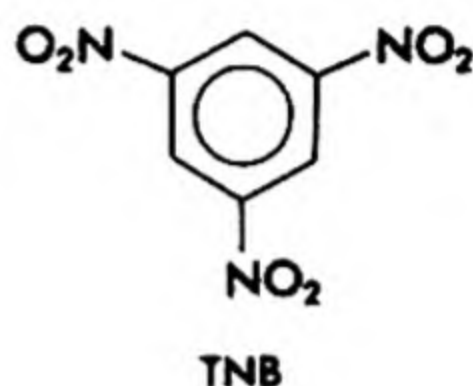
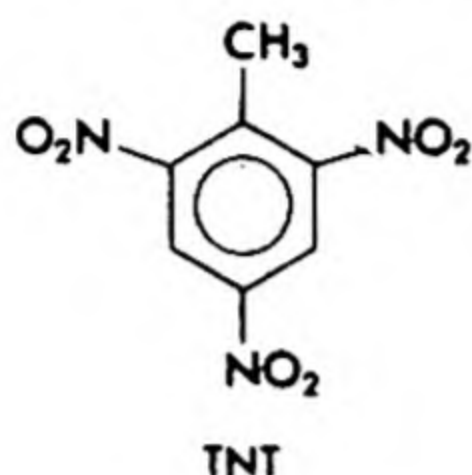
Oxidized nitrogen functions are also common in organic chemistry. Of these, the most important is the nitro group, NO_2 . Aromatic nitro compounds are prepared by treatment of suitable hydrocarbons with a "nitrating mixture" of concentrated nitric and concentrated sulfuric acids.



Aliphatic nitro compounds can be prepared by displacement reactions of alkyl halides.



Compounds with several nitro groups are often used as high explosives. Examples are 2,4,6-trinitrotoluene (TNT) and trinitrobenzene (TNB).

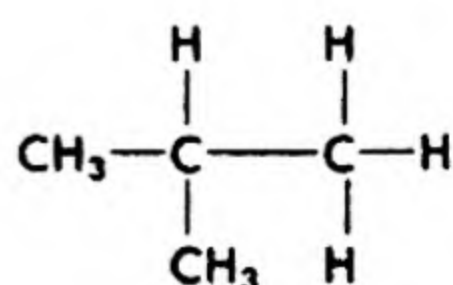
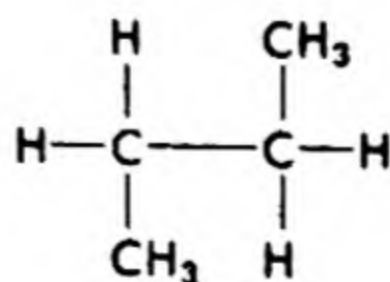
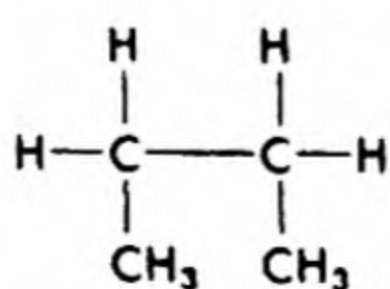
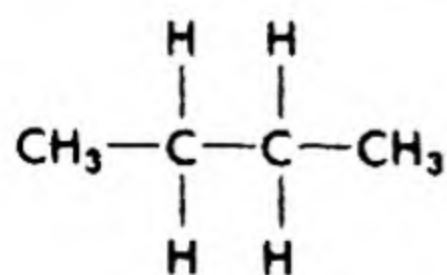


SUPPLEMENTARY READINGS

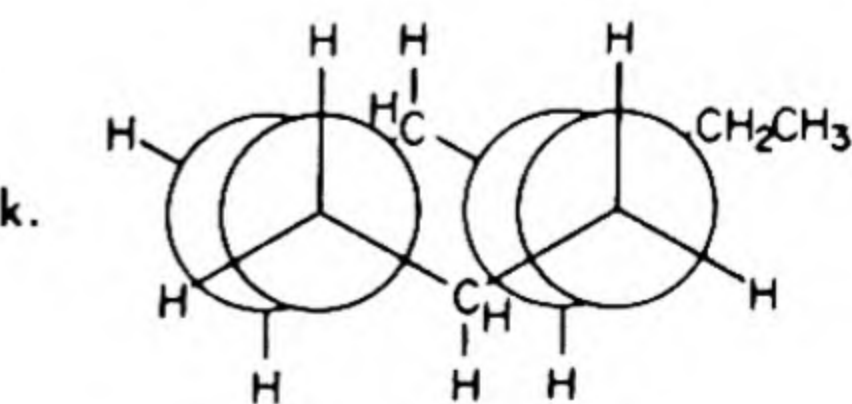
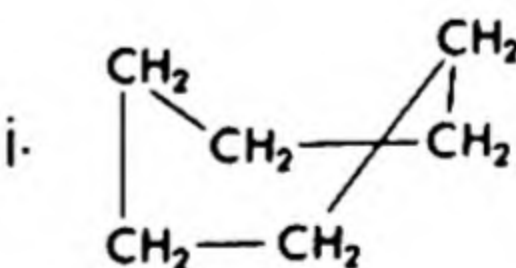
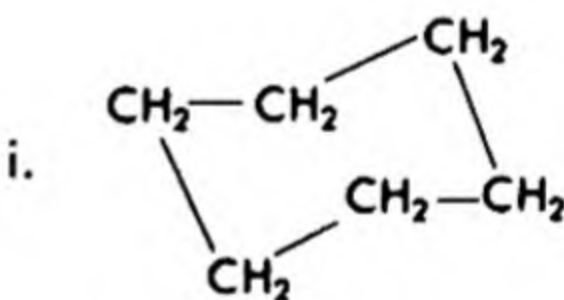
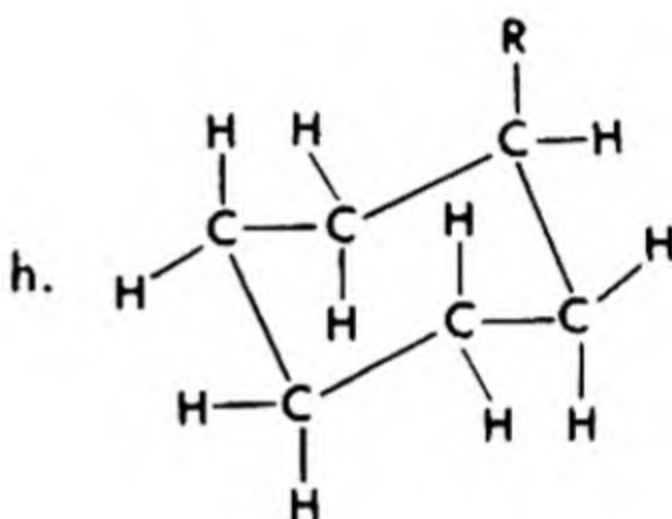
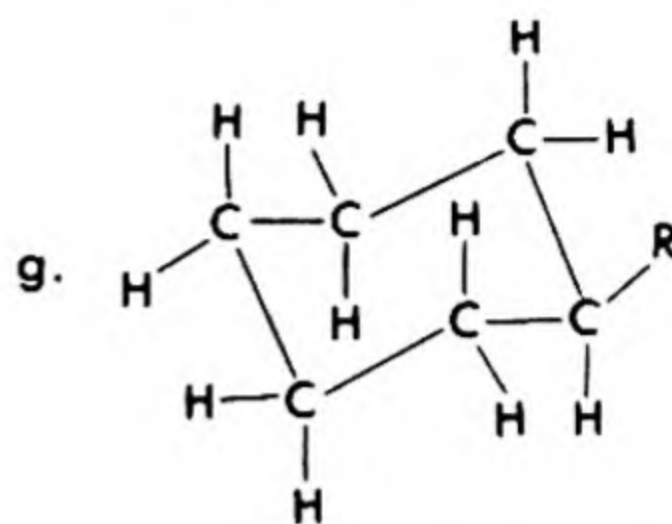
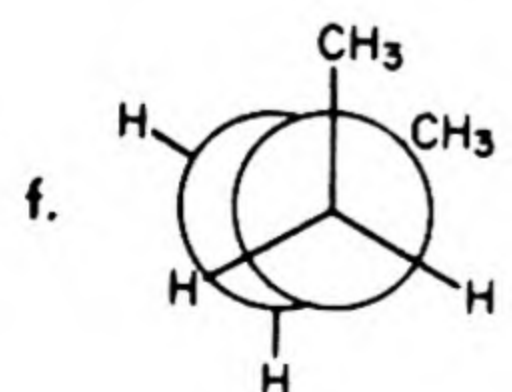
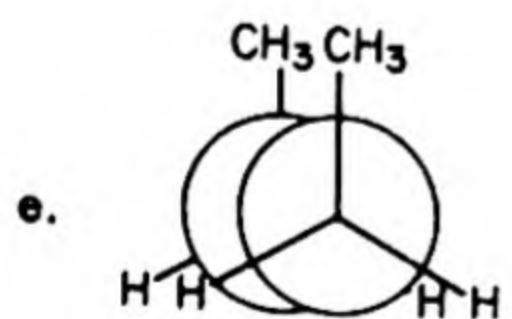
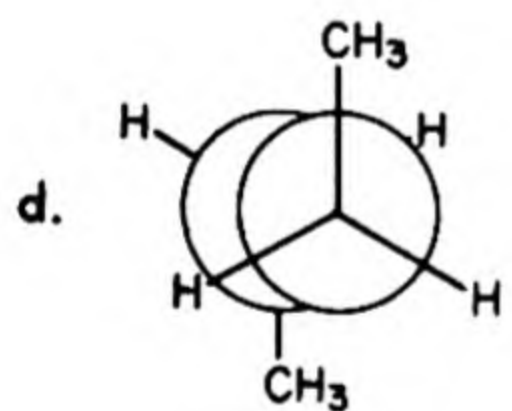
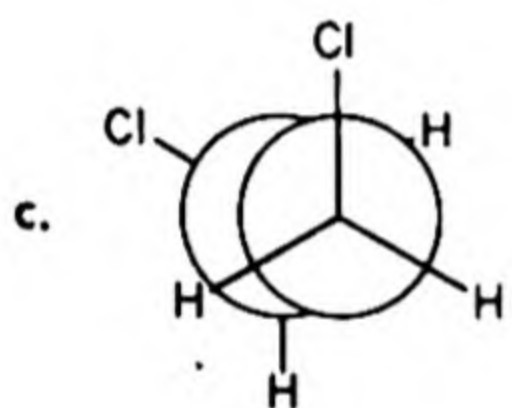
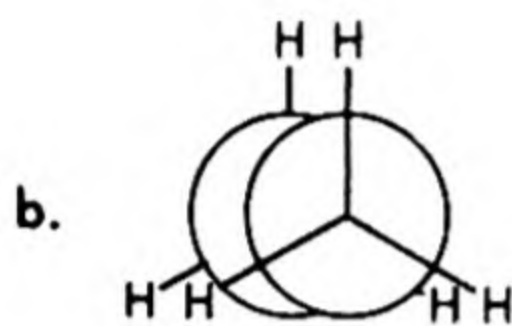
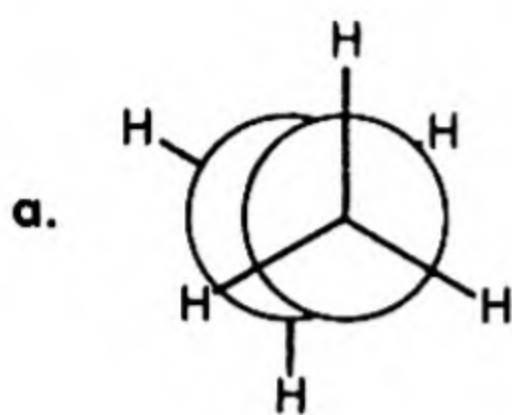
- Dauben, W. G., and K. S. Pitzer, Chapter 1 in M. S. Newman, *Steric Effects in Organic Chemistry*, Wiley, New York, 1956.
- Eliel, E. L., "Conformational Analysis in Mobile Systems," *J. Chem. Educ.*, **37**, 126-133 (1960).
- Eliel, E. L., *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962, Chapters 7, 8, 9.
- Herz, W., *The Shape of Carbon Compounds*, Benjamin, New York, 1963, Chapters I, II, III, IV.
- Ryschkewitsch, G. E., *Chemical Bonding and the Geometry of Molecules*, Reinhold, New York, 1963.
- Wilson, A., and D. Goldhamer, "Cyclobutane Chemistry. 1. Structure and Strain Energy," *J. Chem. Educ.*, **40**, 504-511 (1963).

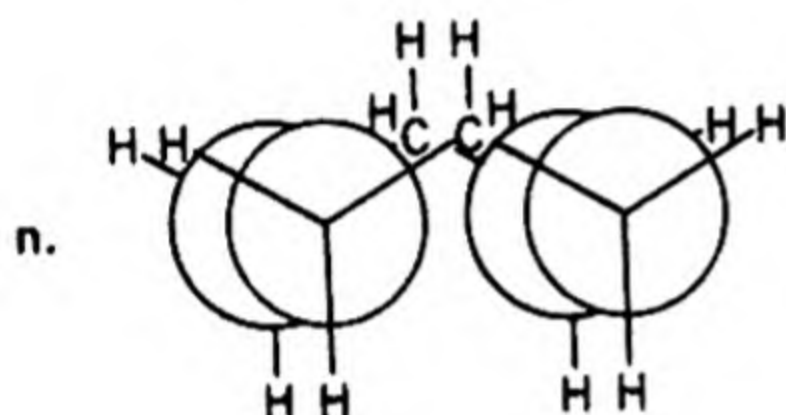
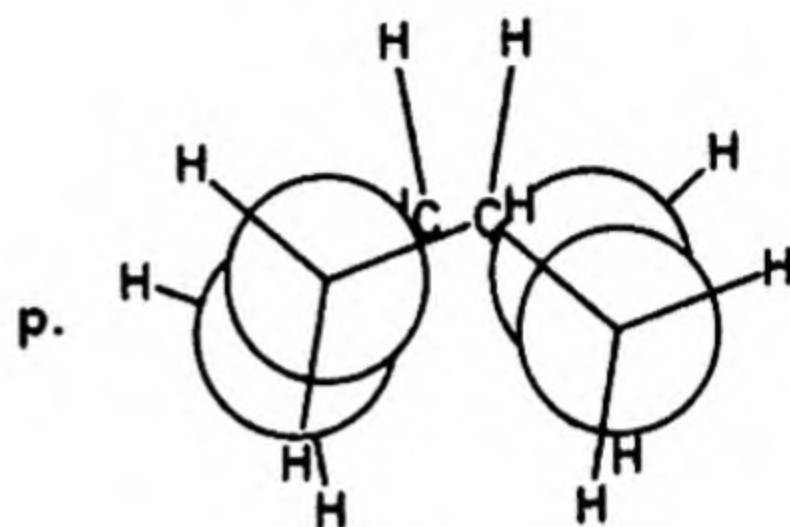
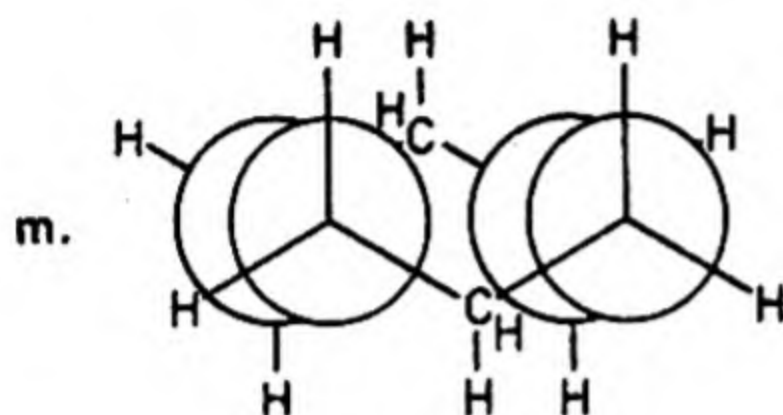
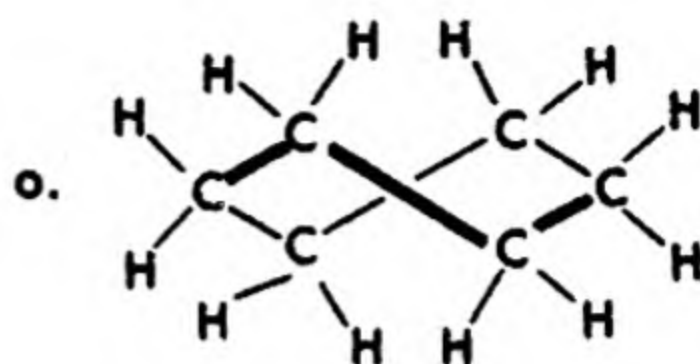
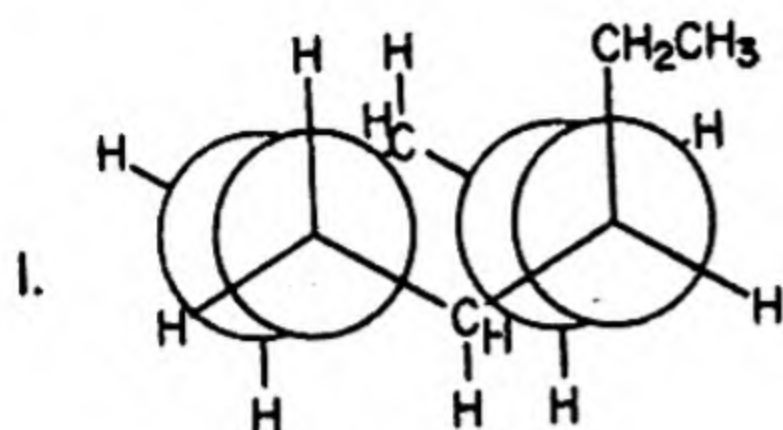
QUESTIONS AND PROBLEMS

- What is an alkane? Give a synonym and a type structure. Give a synonym for alkene, alkyne.
- What does the term alkyl mean? Give an example.
- Illustrate the following using structural formulas:
 - homologs
 - carbon-chain isomers
 - positional isomers
 - functional group isomers
- Show which of the following formulas represent identical compounds and which represent isomers:



5. Define saturated, unsaturated. Give examples.
6. What is a ring compound? Give an example.
7. Name the conformation of each of the following formulas.





8. What are aliphatic hydrocarbons? alicyclic hydrocarbons?
 9. What are important sources of arenes?
 10. Deduce the molecular formula of a compound which provides the following data.

Analysis: C, 67.90%; H, 11.2%. A sample of 5.38 g. of the compound occupies 693 ml. at 0° and 760 mm. The compound gives a positive test for halogen.

What further information is needed to assign a structure to the compound?

11. What is a functional derivative of a carboxylic acid? Write structural formulas for four types.

12. Write a structural formula for an actual compound to illustrate each of the following:

- a. primary amine
 b. primary ammonium salt
 c. secondary amine

- d. tertiary amine
 e. quaternary ammonium salt

13. Show how the *t*-butyl group could be used to "lock" a hydroxy group in axial or equatorial conformation in a chair-cyclohexane ring.

6

Nomenclature

6-1 TRIVIAL NAMES

In the infancy of organic chemistry, relatively few organic compounds were known. These were often named at the whims of their discoverers, sometimes on the basis of a biochemical or chemical source, sometimes because of a property, and rarely on the basis of structure. These names, which generally involved no attempt at systematization, nevertheless became widely used *common* or *trivial* names.

TABLE 6-1. Examples of Common Names

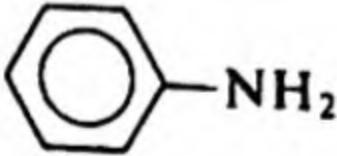
Structures	Names
FROM SOURCES	
$\begin{array}{c} \text{H}_2\text{N}-\text{C}-\text{NH}_2 \\ \parallel \\ \text{O} \end{array}$	urea (from urine)
	aniline (derived from anil, or indigo, a dye)
$\begin{array}{c} \text{CH}_3\text{CCH}_3 \\ \parallel \\ \text{O} \end{array}$	acetone (derived from acetic acid)
FROM PROPERTIES	
$\begin{array}{c} \text{CH}=\text{O} \\ \\ \text{H}-\text{C}-\text{OH} \\ \\ \text{HO}-\text{C}-\text{H} \\ \\ \text{H}-\text{C}-\text{OH} \\ \\ \text{H}-\text{C}-\text{OH} \\ \\ \text{CH}_2\text{OH} \end{array}$	glucose (from Gk. <i>glykys</i> , sweet)

TABLE 6-1. (Continued)

Structures	Names
$\begin{array}{c} \text{CH}_2\text{—OH} \\ \\ \text{CH—OH} \\ \\ \text{CH}_2\text{—OH} \end{array}$	glycerol (also from <i>glykys</i>)
$\text{H}_2\text{C=CH}_2$	olefine (from F. <i>olefiant</i> , oil-forming) (now ethylene)
$\begin{array}{c} \text{O} \\ // \\ \text{CH}_3\text{C} \\ \backslash \\ \text{OH} \end{array}$	acetic acid (from Lat.: <i>acetum</i> , vinegar, and <i>acidum</i> , sour, both from <i>acere</i> , to be sharp)
FROM STRUCTURES	
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	<i>n</i> -pentane (from Gk. <i>pente</i> , five)
$\text{CH}_3\text{CH}_2\text{I}$	ethyl iodide (ethyl group + iodide)

6-2 EARLY SYSTEMS

As the science of organic chemistry developed, it was soon apparent that the enormous number and variety of organic compounds would become an unmanageable burden to memory unless some relationship between nomenclature and structure were utilized in a systematic manner. Early attempts were often confined to limited classes of compounds, so that significantly different systems applied to different types of compounds.

TABLE 6-2. The Normal Alkanes

Structure	Common Name	IUPAC Name
CH_4	Methane	Methane
$\text{CH}_3\text{—CH}_3$	Ethane	Ethane
$\text{CH}_3\text{—CH}_2\text{—CH}_3$	Propane	Propane
$\text{CH}_3\text{—CH}_2\text{—CH}_2\text{—CH}_3$	<i>n</i> -Butane	Butane
$\text{CH}_3\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—CH}_3$	<i>n</i> -Pentane	Pentane
$\text{CH}_3\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—CH}_3$	<i>n</i> -Hexane	Hexane
$\text{CH}_3\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—CH}_3$	<i>n</i> -Heptane	Heptane
$\text{CH}_3\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—CH}_3$	<i>n</i> -Octane	Octane
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	<i>n</i> -Nonane	Nonane
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	<i>n</i> -Decane	Decane

Paraffin hydrocarbons were early systematized (beyond the first four, which have common names) by the use of numerical roots and the suffix *-ane*. These names, which are repetitive in the same way as cardinal numbers, form the basis of the most modern and most inclusive system, developed by the International Union of Pure and Applied Chemistry. The importance of these names to the IUPAC system requires the learning of Tables 6-2 and 6-3.

TABLE 6-3. System of Naming Higher Alkanes

Prefixes			Full Name	Number of Carbon Atoms
Units	Tens	Hundreds		
Un, 1	Dec, 10	—	Undecane	11
Do, 2		—	Dodecane	12
Tri, 3		—	Tridecane	13
Tetra, 4		—	Tetradecane	14
Penta, 5		—	Pentadecane	15
Hexa, 6		—	Hexadecane	16
Hepta, 7		—	Heptadecane	17
Octa, 8		—	Octadecane	18
Nona, 9		—	Nonadecane	19
—	Eicos, 20	—	Eicosane	20
Un	Eicos	—	Uneicosane	21
—	Triacont, 30	—	Triacontane	30
—	Tetracont, 40	—	Tetracontane	40
—	Pentacont, 50	—	Pentacontane	50
—	Hexacont, 60	—	Hexacontane	60
—	Heptacont, 70	—	Heptacontane	70
—	Octacont, 80	—	Octacontane	80
—	Nonacont, 90	—	Nonacontane	90
—	—	Cent, 100	Centane	100
Tri	Pentacont	Cent	Tripentacontacentane	153

Common names of alkanes utilize prefixes to designate certain chain types, as *normal* (*n*-) for continuous chains, *iso* (*i*-) for chains with a terminal methyl branch, and *neo* for chains with a terminal dimethyl branch. Examples are in Table 6-4.

Some other types of systems, fragments of which often appear even in current nomenclature, are constitutive names (naming of constituent parts

TABLE 6-4. Some Branched Alkanes

Structure	Common Names	IUPAC Name
$\begin{array}{c} \text{CH}_3-\text{CH}-\text{CH}_3 \\ \\ \text{CH}_3 \end{array}$	Isobutane	2-Methylpropane
$\begin{array}{c} \text{CH}_3-\text{CH}-\text{CH}_2-\text{CH}_3 \\ \\ \text{CH}_3 \end{array}$	Isopentane	2-Methylbutane
$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{C}-\text{CH}_3 \\ \\ \text{CH}_3 \end{array}$	Neopentane	2,2-Dimethylpropane
$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{C}-\text{CH}_2-\text{CH}_3 \\ \\ \text{CH}_3 \end{array}$	Neohexane	2,2-Dimethylbutane
$\begin{array}{c} \text{CH}_3-\text{CH}-\text{CH}-\text{CH}_3 \\ \quad \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$	Diisopropyl	2,3-Dimethylbutane
$\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \quad \\ \text{CH}_3-\text{C}-\text{CH}_2-\text{CH}-\text{CH}_3 \\ \\ \text{CH}_3 \end{array}$	Commercial isooctane	2,2,4-Trimethylpentane

of molecules), substitution names (alkyl substitution of a parent compound), additive names (naming of molecules from substances which combine to form them), derivative names (naming of one compound because of its relationship to another), and generic names (based on classes or types). Pure examples are difficult to find, since even constitutive and substitution names tend to be derivative in the sense that the constituent parts are often named as derived from other substances (e.g., hydrocarbon groups from the related hydrocarbons). Some examples which are representative of general application in a given class of compounds are shown in Table 6-5.

Besides the naming of the gross features of compounds, the problem of allocation of substituents produced many systems. Prefixes, Greek letters, and numerals were used, often in several different ways. Again, examples which are representative of general application are shown (Table 6-6).

TABLE 6-5. Examples of Systems for Common Names

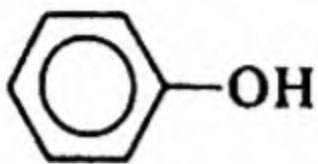
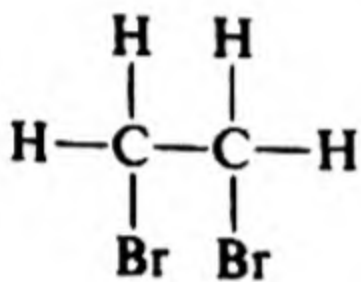
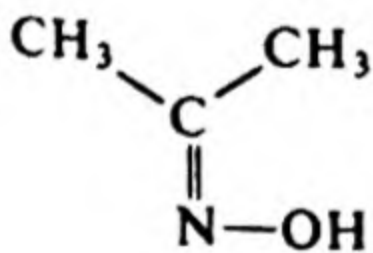
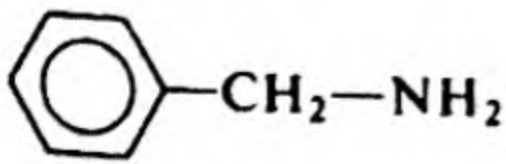
Structures	Names
CONSTITUTIVE NAMES	
$\text{CH}_3\text{CH}_2\text{Br}$	ethyl bromide
	phenol (phenyl + -ol)
$\text{HC}-\text{O}-\text{CH}_2\text{CH}_3$ \parallel O	ethyl formate
SUBSTITUTION NAMES	
$\text{CH}_3-\text{C}\equiv\text{CH}$	methylacetylene
$\text{CH}_3-\text{NH}-\text{CH}_3$	dimethylamine (amine = ammonia)
ADDITIVE NAMES	
	ethylene bromide
CH_3-CH $\swarrow \quad \searrow$ $\text{OH} \quad \text{NH}_2$	acetaldehyde ammonia
DERIVATIVE NAMES	
$\text{CH}_3\text{CH}=\text{O}$	acetaldehyde (related to acetic acid)
CH_3CNH_2 \parallel O	acetamide
	acetoxime (oxime of acetone)
GENERIC NAMES	
$\text{CH}_3\text{CH}_2\text{OH}$	ethyl alcohol
$\text{CH}_3\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_3$	ethyl ether
$\text{CH}_3-\text{C}-\text{CH}_2\text{CH}_3$ \parallel O	methyl ethyl ketone
	benzylamine (amine = class; see also substitution names)

TABLE 6-6. Positioning Systems

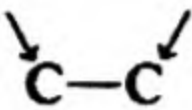
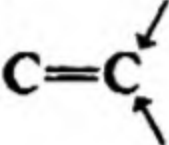
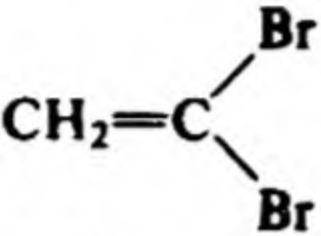
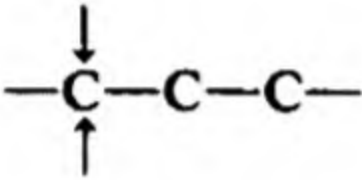
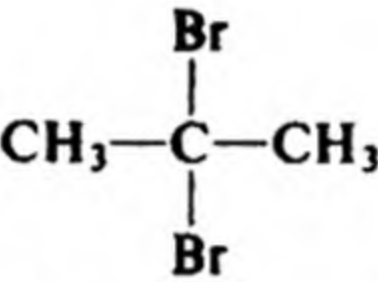
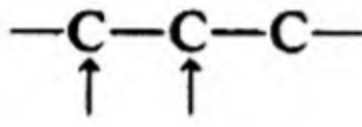
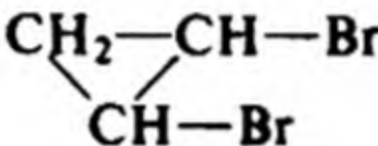
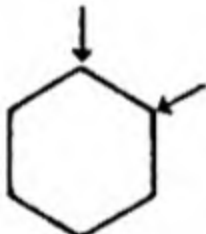
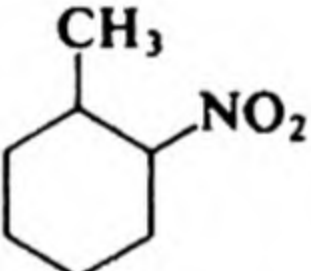
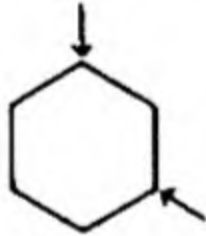
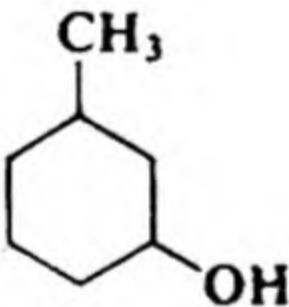


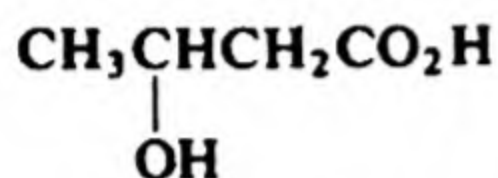
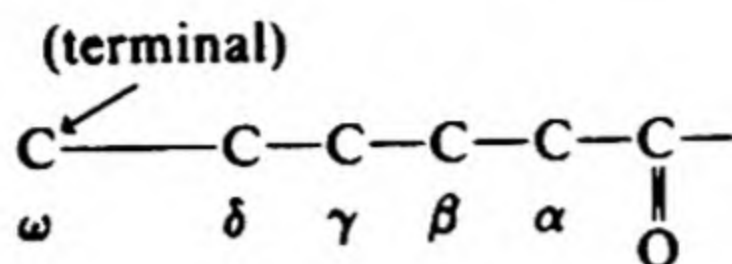
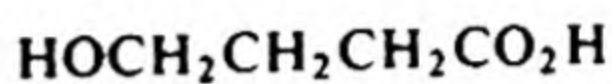
Positions	Prefixes
	$\text{Br}-\text{CH}=\text{CH}-\text{Br}$ <p><i>sym</i>-dibromoethylene</p> <p>symmetrical (<i>sym</i>-)</p>
	 <p><i>unsym</i>-dibromoethylene</p> <p>unsymmetrical (<i>unsym</i>-)</p>
	 <p>a <i>gem</i>-dibromide</p> <p>geminal (<i>gem</i>-)</p>
	 <p>vicinal (<i>vic</i>-)</p>
	 <p><i>o</i>-nitrotoluene</p> <p>ortho (<i>o</i>-)</p>
	 <p><i>m</i>-nitrotoluene</p> <p>meta (<i>m</i>-)</p>
	 <p><i>p</i>-nitrotoluene</p> <p>para (<i>p</i>-)</p>

TABLE 6-6. (Continued)

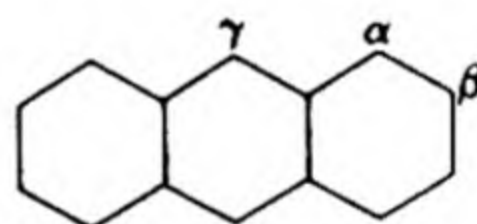
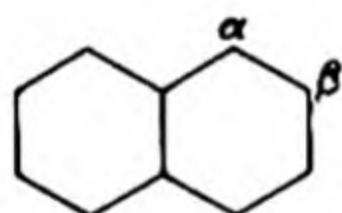
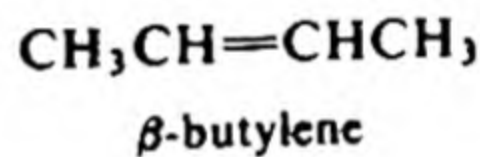
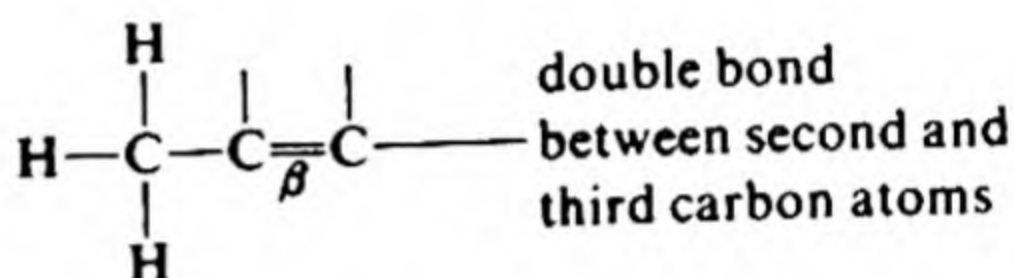
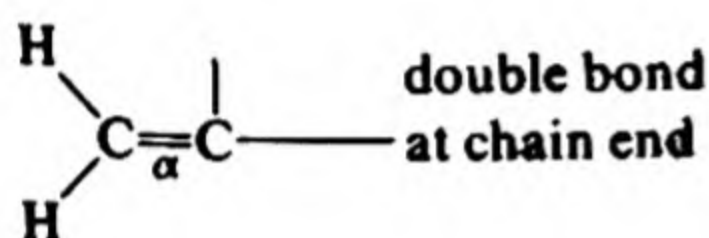
GREEK LETTER CONVENTIONS



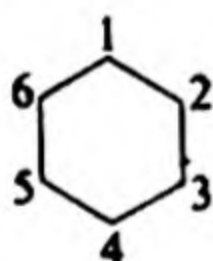
β -hydroxy-*n*-butyric acid



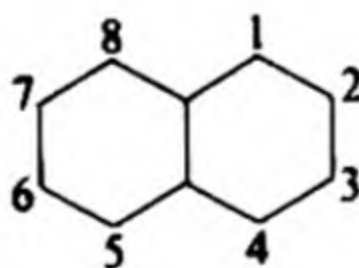
γ -hydroxybutyric acid
(ω -hydroxybutyric acid)



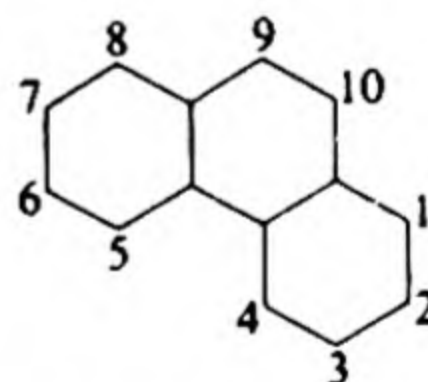
NUMERICAL CONVENTIONS



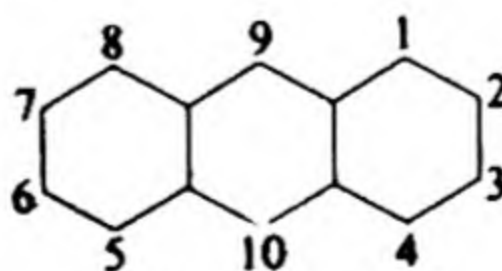
benzene ring



naphthalene ring



phenanthrene ring



anthracene ring

6-3 THE IUPAC SYSTEM

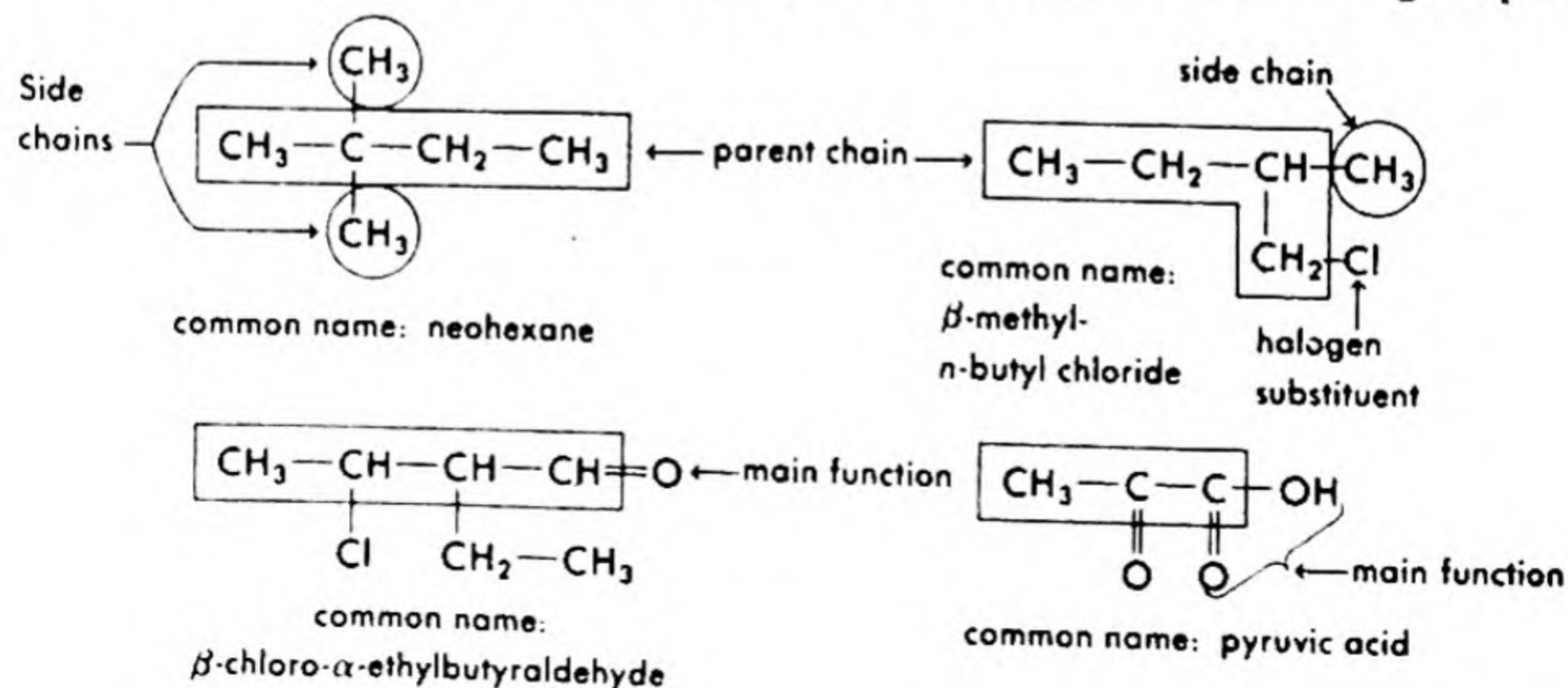
The growing confusion in the chemical literature which resulted from the use of such a variety of common and systematic names (some of them incorrect, such as nitroglycerin for glyceryl nitrate, which is not a nitro compound) stimulated a group of chemists to convene at Geneva in 1892 to devise a system of nomenclature that would be consistent, unambiguous, and clearly related to structure. A system of verbal structures was set up, which was revised and extended in 1930 at the Liege meeting of the International Union of Chemistry (now the International Union of Pure and Applied Chemistry, or IUPAC). At this meeting a permanent nomenclature committee was established to make such further rules as should be necessary to the nomenclature of both organic and inorganic chemistry. The committee serves two functions: to extend the rules of systematic nomenclature to new classes or modify existing rules, and to sanction the usage of the best common or trivial names in keeping with accepted nomenclature practices.

The complete rules for the IUPAC system are found only by reference to all of the following sources, with the later ones superseding some portions of the earlier ones:

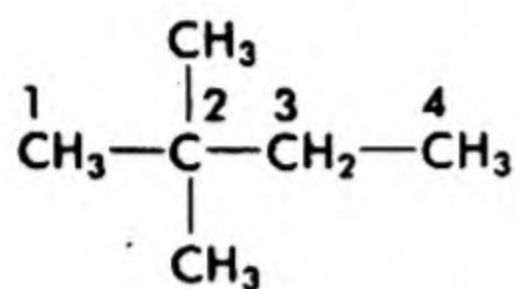
1. *J. Am. Chem. Soc.* **55**, 3905-25 (1933) or *Handbook of Chemistry and Physics*, Chemical Rubber Publishing Co., Cleveland, Ohio.
2. "Comptes Rendus de la Quinzième Conference; Commission de Nomenclature de Chimie Organique" (Reprints available from the American Chemical Society).
3. *J. Am. Chem. Soc.* **82**, 5545-74 (1960) or "IUPAC Nomenclature of Organic Chemistry 1957," Butterworths Scientific Publications (1958).

The IUPAC rules are easier to apply than to state, so the system is developed here largely through the use of examples.

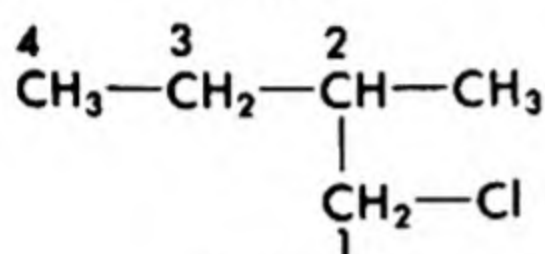
A compound to be named is divided into the longest continuous chain with the main function, called the *parent* (or fundamental) chain, and all of the remaining groups along it, called *side chains* or *substituent groups*.



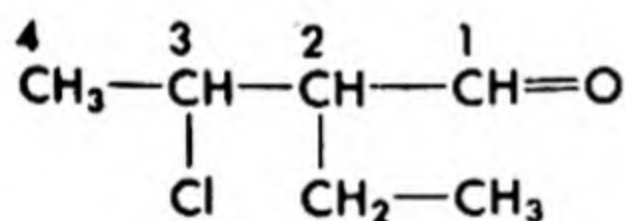
The parent chain is next numbered from one end to the other to provide lowest numbers (a) at the main function, (b) at double bonds, (c) at triple bonds, or (d) at substituent groups, in this order of preference. Where several groups are involved, lowest numbers means (a) lowest sum of numbers, (b) lowest individual numbers, (c) lowest numbers for first-named groups, in this order of preference.



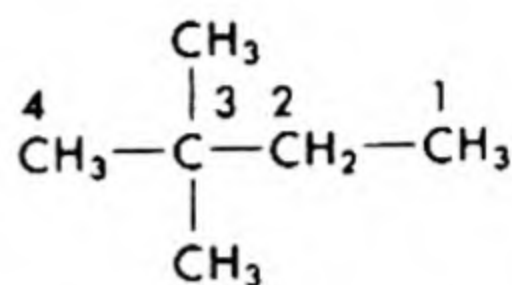
correct



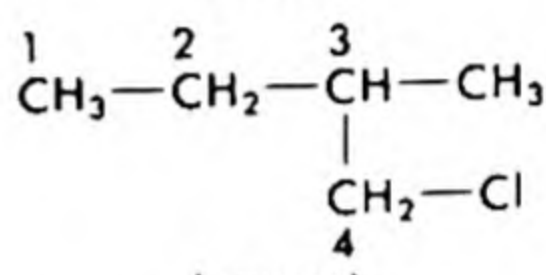
correct



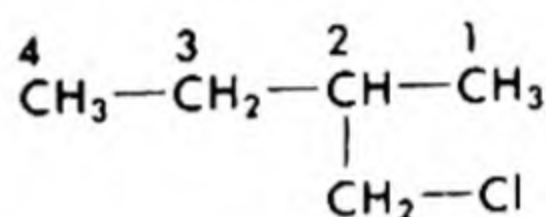
correct



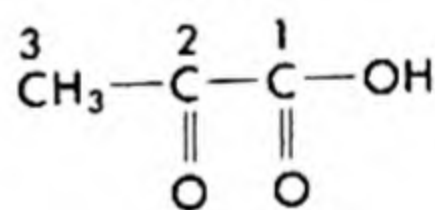
incorrect



incorrect

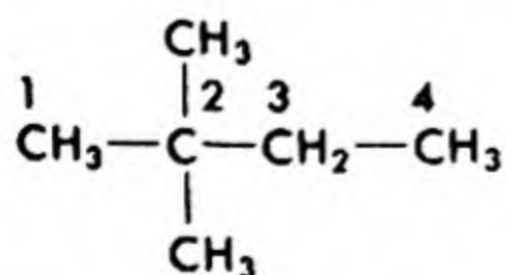


incorrect



correct

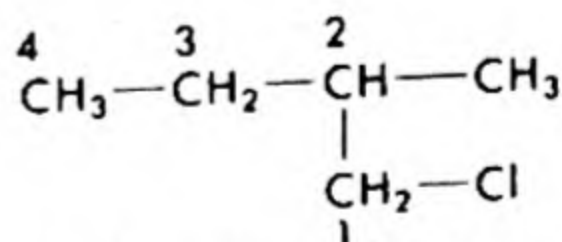
The substituent groups are named in alphabetical order, each preceded by the position number of the carbon atom to which it is attached, and a numerical prefix (di-, tri-, tetra-, penta-, ...) to indicate its multiplicity. Every group must have a number for each occurrence. These are followed by the root of the parent chain, based on the alkane of the same number of carbon atoms (meth-, eth-, prop-, but-, pent-, hex-, ...) and the suffix or suffixes which designate multiple bonds and the main function. Group prefixes and functional suffixes are given in Table 6-7.



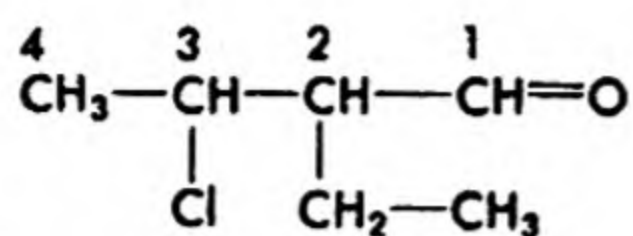
2,2 — di — methyl — but — ane

positions (separated by commas)	multi- plicity prefix	substituent name	root	alkane suffix
---------------------------------------	-----------------------------	---------------------	------	------------------

2,2-dimethylbutane

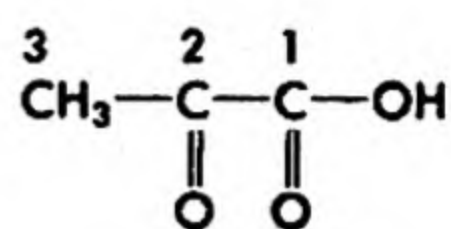


1-chloro-2-methylbutane



3-chloro-2-ethylbutanal

alkane functional
suffix suffix



2-oxopropanoic acid

functional
suffix

TABLE 6-7. Substituent Prefixes and Functional Suffixes

Group	Suffix (when main function)	Prefix (when substituent)
saturated parent chain	-ane (-an- before functional suffix with initial vowel)	
$\begin{array}{c} \diagup \\ \text{C}=\text{C} \\ \diagdown \end{array}$	-ene (-en- before functional suffix with initial vowel)	
$-\text{C}\equiv\text{C}-$	-yne (-yn- before functional suffix with initial vowel)	
$-\text{F}$		fluoro
$-\text{Cl}$		chloro
$-\text{Br}$		bromo
$-\text{I}$		iodo
$-\text{NO}_2$		nitro
$-\text{NO}$		nitroso
$-\text{OR}$		alkyloxy (Substitute name of group R for alkyl , as methoxy, ethoxy, prop- oxy, butoxy, pentyloxy, hexyloxy . . . four lowest members omit -yl- before -oxy)
$-\text{SR}$		alkylthio (substitute name of group R for alkyl , as methylthio)
$-\text{OH}$	-ol	hydroxy
$-\text{SH}$	-thiol	mercapto
$-\text{O}-\text{N}=\text{O}$	nitrite (separate word)	nitrito

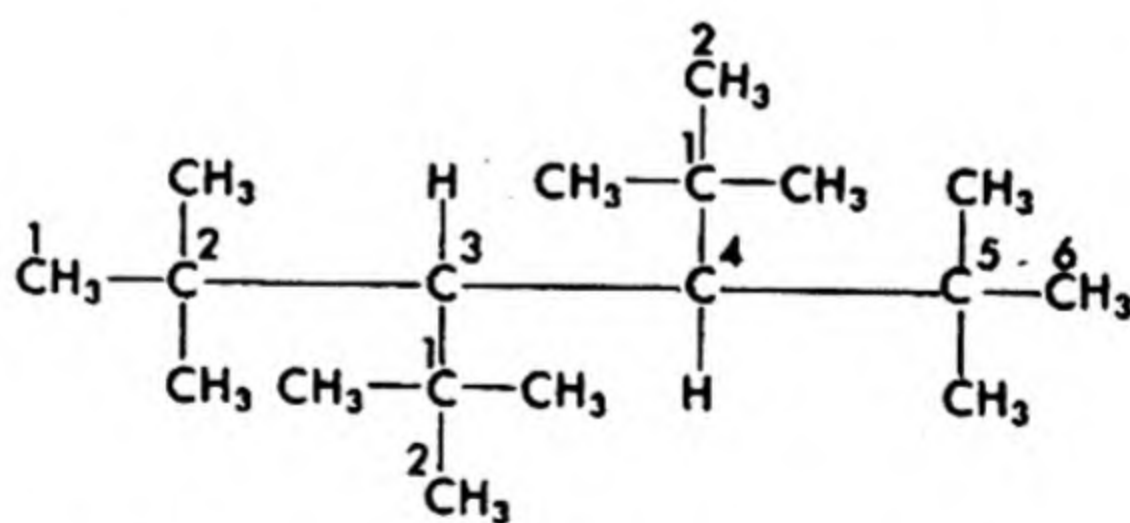
TABLE 6-7. (Continued)

Group	Suffix (when main function)	Prefix (when substituent)
$-\text{O}-\text{NO}_2$	nitrate (separate word)	nitrato
$-\text{NH}_2$	-amine	amino
$\text{R}-\text{NH}-$	-amine	alkylamino (Substitute name of group R for alkyl)
$\text{R}_2\text{N}-$	-amine	dialkylamino (as above)
$\text{RR}'\text{N}-$	-amine	alkylalkyl' amino (as above)
$-\text{NH}_3^+$, $-\text{NRH}_2^+ \dots$ $-\text{NR}_3^+$	-ammonium	
$-\text{N}=\text{C}=\text{O}$	isocyanate (separate word)	isocyanato
$-\text{N}=\text{C}=\text{S}$	isothiocyanate (separate word)	isothiocyanato
$-\text{CH}=\text{O}$	-al (part of parent chain) -carbaldehyde (not part of parent chain)	formyl
$=\text{O}$	-al (at chain end; see above) -one (not at chain end)	oxo oxo
$\begin{array}{c} -\text{COH} \\ \\ \text{O} \end{array}$	-oic acid (part of parent chain) -carboxylic acid (not part of parent chain)	carboxy
$\begin{array}{c} -\text{C}-\text{O}^- \\ \\ \text{O} \end{array}$	-oate (part of parent chain) -carboxylate (not part of parent chain)	
$\begin{array}{c} -\text{C}-\text{OR} \\ \\ \text{O} \end{array}$	alkyl [root]oate (see above) alkyl [root]carboxylate (see above) Name of alkyl group is separate word	alkyloxycarbonyl (Substitute name of group R for alkyl , as methoxycarbonyl, ethoxycarbonyl, pentyloxycarbonyl, Four lowest members omit -yl- before -oxy-)
$\begin{array}{c} -\text{C}-\text{Cl} \\ \\ \text{O} \end{array}$	-oyl chloride (part of parent chain) -carbonyl chloride (not part of parent chain)	chloroformyl

TABLE 6-7. (Continued)

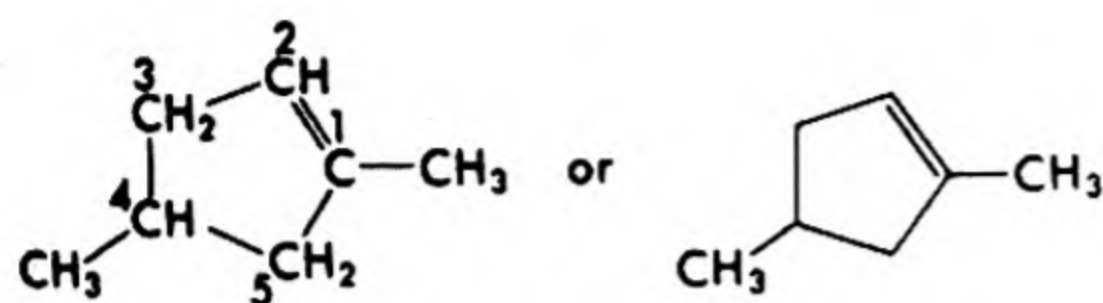
Group	Suffix (when main function)	Prefix (when substituent)
$\begin{array}{c} \text{—C—NH}_2 \\ \\ \text{O} \end{array}$	-amide (part of parent chain) -carbonamide (not part of parent chain)	carbamoyl
$\begin{array}{c} \text{—C—NHR} \\ \\ \text{O} \end{array}$	<i>N</i> -alkyl[root]amide	<i>N</i> -alkylcarbamoyl (substitute name of group R for alkyl)
$\begin{array}{c} \text{NH}_2 \\ \diagup \\ \text{—C} \\ \diagdown \\ \text{NH} \end{array}$	-amidine (part of parent chain) -carbonamidine (not part of parent chain)	amidino
$\text{—C}\equiv\text{N}$	onitrile (part of parent chain) -carbonitrile (not part of parent chain)	cyano
$\text{—SO}_2\text{—OH}$	-sulfonic acid	sulfo
—SO_3^-	-sulfonate	

Complex groups named as substituted groups use prefixes bis, tris, tetrakis, pentakis, ... instead of di, tri, tetra, penta, ... to indicate multiplicity.



3,4-bis(1,1-dimethylethyl)-2,2,5,5-tetramethylhexane

Ring systems, exclusive of any side chains, are considered parent systems. The simple ring compounds are numbered in sequence around the ring so as to allocate low numbers according to the usual principles. Substituent groups that occur alone and certain main functions need not be numbered, since these are automatically in the number one position. Polycyclic compounds, however, have fixed numbering systems, as described in *The Ring Index* (Appendix I-3). The following examples demonstrate some of the principles.

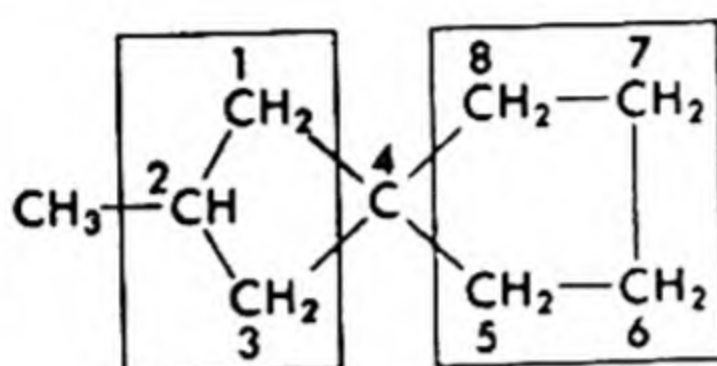


1,4-dimethylcyclopentene
(number from double bond as 1)



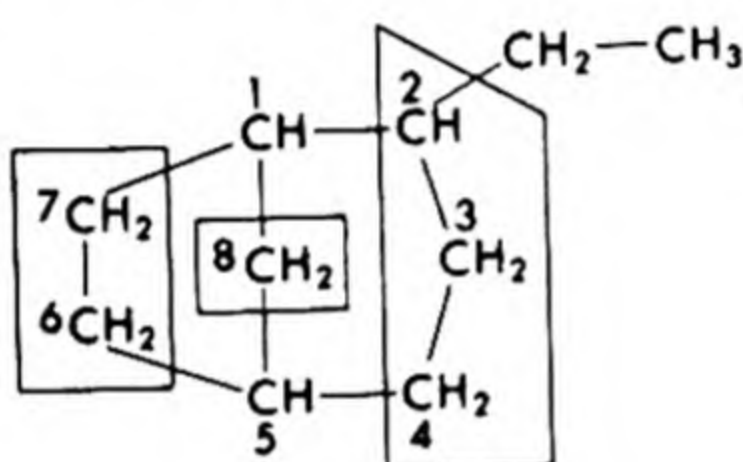
nitrobenzene
(single substituent is not numbered)

three
carbon
atoms
between ring
junction

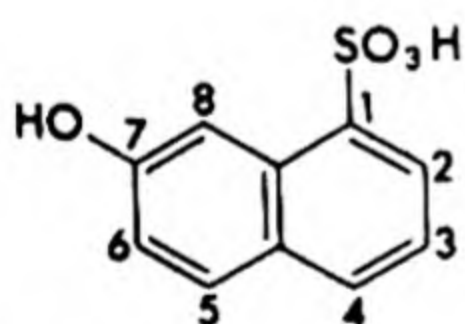


four atoms
between ring
junction

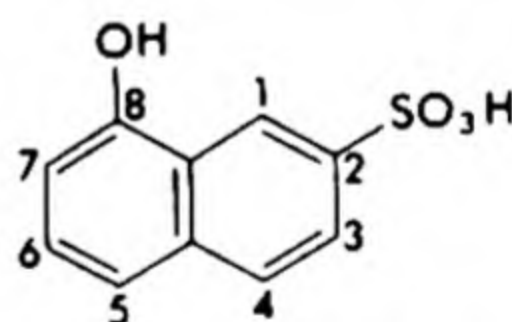
2-methylspiro [3.4] octane
(direction of numbering gives spiro atom lower number)



2-ethylbicyclo [3.2.1] octane
(direction of numbering gives largest bridge lowest numbers, smallest bridge highest numbers; numbering starts at bridgehead)

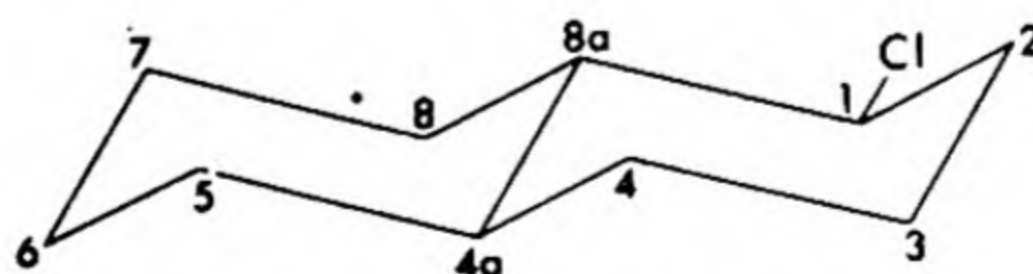


7-hydroxynaphthalene-1-sulfonic acid



8-hydroxynaphthalene-2-sulfonic acid

(fixed numbering system determining position number; lowest possible assigned to main function)



trans-1-chloro-*trans*-decahydronaphthalene

(Irregular; named as a hydroaromatic compound instead of a bicyclo compound. This is the rule for all polycyclic hydroaromatic compounds.)

(Fixed numbering system determines number for substituent—lowest possible)

Other examples of IUPAC nomenclature as well as common and *Chemical Abstracts* nomenclatures are given in the nomenclature tables after the next section and in Appendix III.

6-4 CHEMICAL ABSTRACTS NOMENCLATURE

The official nomenclature of the American Chemical Society as utilized in *Chemical Abstracts* is summarized in the 1945 subject index issue of that publication. The IUPAC system is used in large measure. Where the two differ, the *Chemical Abstracts* usage is generally one of the better of the earlier systems, or a widely accepted common name. *Chemical Abstracts* names different from common or IUPAC names are marked ^{CA} in the tables.

6-5 NOMENCLATURE TABLES

It is not intended that the student should memorize all of the names in the following tables. He should practice and become familiar with the various systems and use these as the means of constructing names. However, many common names must be memorized, since they often do not belong to systems. Such common names are given frequently under their structures throughout the book to aid in this memorization. Appendix III is arranged in alphabetical order of common names, hence can serve as a glossary for frequent reference.

In the following tables, an asterisk (*) denotes a common name sanctioned by the IUPAC. Nonsystematic common names are in boldface.

TABLE 6-8. Hydrocarbon Groups

Common Name	Structure	IUPAC Rules Name
acetal	$\text{CH}_3\text{CH}=\text{}$	ethylidene
acetylenyl	$\text{HC}\equiv\text{C}-$	ethynyl
allyl*	$\text{CH}_2=\text{CH}-\text{CH}_2-$	2-propenyl
amyl		
<i>n</i> -	$\text{CH}_3(\text{CH}_2)_4-$	pentyl
iso-	$(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2-$	3-methylbutyl
<i>t</i> -	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{CH}_2\text{C}- \\ \\ \text{CH}_3 \end{array}$	1,1-dimethylpropyl

TABLE 6-8. (Continued)

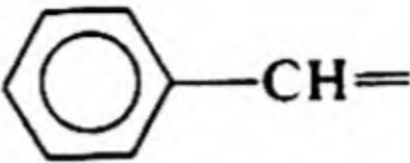
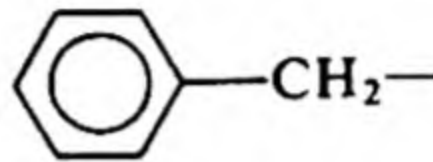
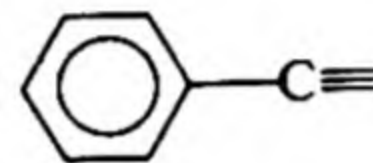
Common Name	Structure	IUPAC Rules Name
benzal benzylidene ^{CA}		phenylmethyldene .
benzyl		phenylmethyl
benzylidyne		phenylmethyldyne
<i>n</i> -butyl	CH ₃ CH ₂ CH ₂ CH ₂ —	butyl
<i>sec</i> -butyl* 2° - also used for <i>sec</i> -	CH ₃ CH ₂ CH— CH ₃	1-methylpropyl
<i>tert</i> -butyl* 1- and 3° - also used for <i>tert</i> -	CH ₃ —C— CH ₃	1,1-dimethylethyl
crotyl (<i>cis</i> or <i>trans</i>)	CH ₃ CH=CHCH ₂ —	2-butenyl (<i>cis</i> or <i>trans</i>)
ethyl	CH ₃ —CH ₂ —	ethyl
ethylene (ethano in bridges)	—CH ₂ —CH ₂ —	ethylene (ethano in bridges)
isobutyl*	CH ₃ CH—CH ₂ — CH ₃	2-methylpropyl
isopropyl*	CH ₃ CH— CH ₃	1-methylethyl
methyl	CH ₃ —	methyl
methylacetylenyl	CH ₃ —C≡C—	1-propynyl
β-methylallyl	CH ₂ =C—CH ₂ — CH ₃	2-methyl-2-propenyl

TABLE 6-8. (Continued)



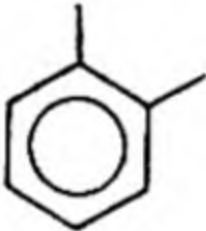
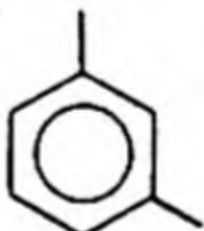

Common Name	Structure	IUPAC Rules Name
methylene (methano in bridges)	$\text{—CH}_2\text{—}$	methylene (methano in bridges)
methylidene methylene ^{CA}	$\text{CH}_2=$	methylidene
neopentyl	$(\text{CH}_3)_3\text{C—CH}_2\text{—}$	2,2-dimethylpropyl
phenethyl	 $\text{—CH}_2\text{—CH}_2\text{—}$	2-phenylethyl
phenyl	 or $\text{C}_6\text{H}_5\text{—}$ abbreviated Ph- or $\phi\text{—}$	phenyl
phenylene		phenylene
<i>o</i> -		1,2-
<i>m</i> -		1,3-
<i>p</i> -		1,4-
propargyl	$\text{HC}\equiv\text{C—CH}_2\text{—}$	2-propynyl
<i>n</i> -propyl	$\text{CH}_3\text{CH}_2\text{CH}_2\text{—}$	propyl
1,2-propylene*	$\text{CH}_3\text{—CH—}$ $\text{CH}_2\text{—}$	1,2-propane
trimethylene	$\text{—CH}_2\text{—CH}_2\text{—CH}_2\text{—}$	trimethylene 1,3-propane

TABLE 6-8. (Continued)

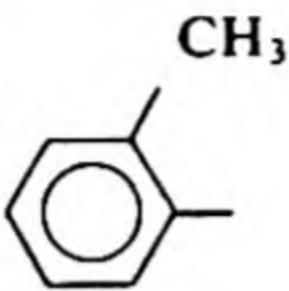
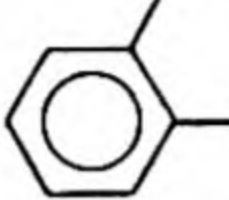
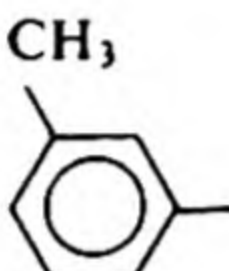
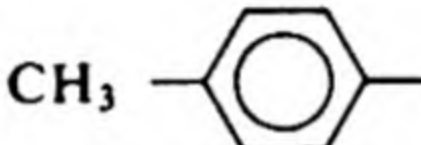
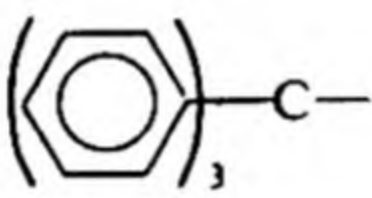
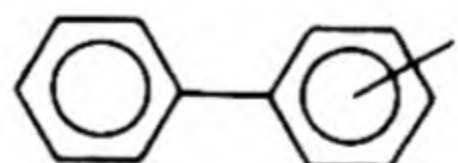
Common Name	Structure	IUPAC Rules Name
tetramethylene	$-(\text{CH}_2)_4-$	tetramethylene 1,4-butane
tolyl*		methylphenyl
<i>o</i> -		2-
<i>m</i> -		3-
<i>p</i> -		4-
trityl		triphenylmethyl
vinyl*	$\text{H}_2\text{C}=\text{CH}-$	ethenyl
vinylene	$-\text{CH}=\text{CH}-$	ethenylene
vinylidene	$\text{H}_2\text{C}=\text{C}=\text{}$	ethenylidene
xenyl biphenylyl ^{CA} (<i>o</i> -, <i>m</i> -, <i>p</i> -)		phenylphenyl (2-, 3-, 4-)

TABLE 6-9. Trivial Roots of Common Names of Acids, Aldehydes, and Their Functional Derivatives

1. ALIPHATIC SATURATED		
Carbon Atoms in Chain	Monocarboxylic	Dicarboxylic
1	form-	—
2	acet-	oxal-
3	propion-	malon-

TABLE 6-9. (Continued)

1. ALIPHATIC SATURATED		
Carbon Atoms in Chain	Monocarboxylic	Dicarboxylic
4	butyr-	succin-
5	valer-	glutar-
6	capro-	adip-
7	enanth-	pimel-
8	capryl-	suber-
9	pelargon-	azela-
10	capr-	sebac-
12	laur-	
14	myrist-	
16	palmit-	(thaps-)
18	stear-	

2. ALIPHATIC UNSATURATED MONOCARBOXYLIC	
Structure	Root
$\text{CH}_2=\text{CH}-\text{C}\begin{array}{l} \text{OH} \\ \text{O} \end{array}$	acryl- (aldehyde: acrolein)
$\begin{array}{c} \text{CH}_3 \quad \text{H} \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \text{C}-\text{OH} \\ \quad \quad \text{O} \end{array}$	<i>trans</i> -croton- (croton-)
$\begin{array}{c} \quad \quad \text{O} \\ \quad \quad \text{O}=\text{C}-\text{OH} \\ \diagup \quad \diagdown \\ \text{CH}_3 \quad \text{C}=\text{C} \\ \diagdown \quad \diagup \\ \text{H} \quad \quad \text{H} \end{array}$	<i>cis</i> -croton- (isocroton-)
$\begin{array}{c} \text{CH}_2 \quad \text{O} \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{CH}_3 \quad \text{C}-\text{OH} \\ \quad \quad \text{O} \end{array}$	methacryl- (aldehyde: methacrolein)
$\text{CH}_3(\text{CH}_2)_7 \begin{array}{c} \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \quad \text{H} \end{array} \begin{array}{c} \text{O} \\ \text{O}=\text{C}-\text{OH} \\ \text{CH}_2 \end{array}$	elaid-

TABLE 6-9. (Continued)

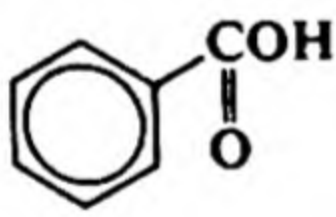
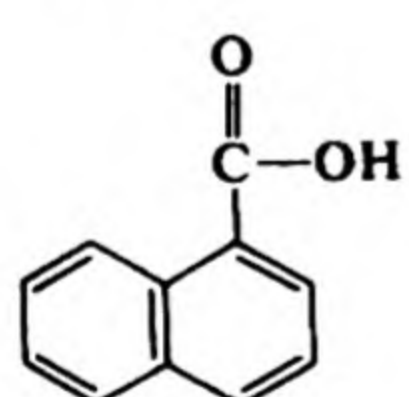
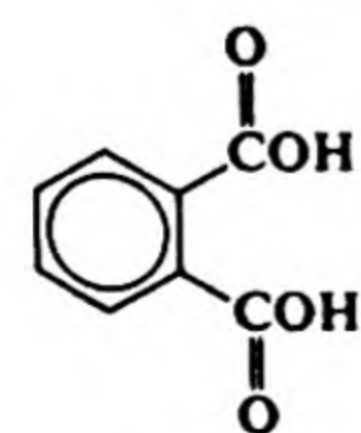
2. ALIPHATIC UNSATURATED MONOCARBOXYLIC	
Structure	Root
$\text{CH}_3(\text{CH}_2)_7 \begin{array}{c} \diagup \\ \text{C} \\ \diagdown \end{array} = \begin{array}{c} \diagdown \\ \text{C} \\ \diagup \end{array} (\text{CH}_2)_7 \text{C}(=\text{O})\text{OH}$	olē- (ē = long e in pronunciation)
$\text{CH}_3(\text{CH}_2)_n \begin{array}{c} \diagup \\ \text{C} \\ \diagdown \end{array} = \begin{array}{c} \diagdown \\ \text{C} \\ \diagup \end{array} (\text{CH}_2)_7 \text{C}(=\text{O})\text{OH}$	$n = 5$: palmitolē- $n = 3$: myristolē- $n = 1$: laurolē-
$\text{CH}_3(\text{CH}_2)_4 \begin{array}{c} \diagup \\ \text{C} \\ \diagdown \end{array} = \text{C}(\text{H})\text{CH}_2\text{C}(\text{H})=\text{C}(\text{H}) (\text{CH}_2)_7 \text{C}(=\text{O})\text{OH}$	linolē-
$\text{CH}_3\text{CH}_2 \begin{array}{c} \diagup \\ \text{C} \\ \diagdown \end{array} = \text{C}(\text{H})\text{CH}_2\text{C}(\text{H})=\text{C}(\text{H})\text{CH}_2\text{C}(\text{H})=\text{C}(\text{H}) (\text{CH}_2)_7 \text{C}(=\text{O})\text{OH}$	linolen-
3. AROMATIC	
Structure of Acid	Root
	benzo-
	α-naphtho-
	phthal-

TABLE 6-9. (Continued)

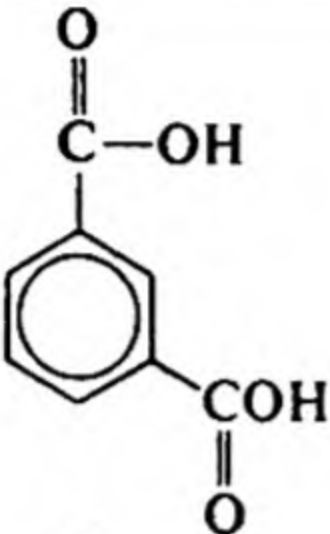

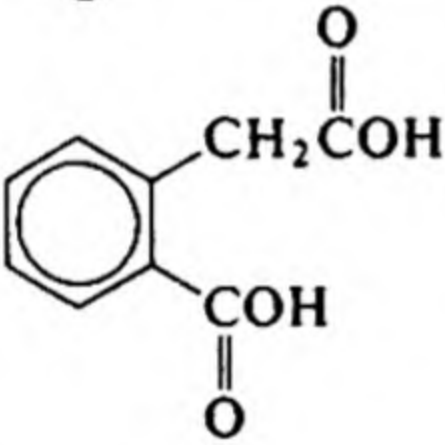
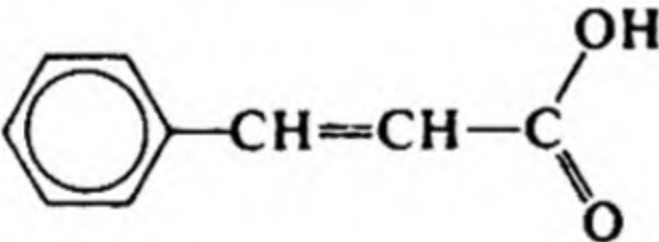
3. AROMATIC	
Structure of Acid	Root
	isophthal-
	terephthal-
	homophthal-
	cinnam-

TABLE 6-10. Examples of Nomenclature in Representative Classes of Compounds

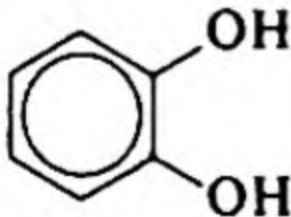
Structure	IUPAC Rules Name	Common Name
$\text{CH}_3\text{CH}(\text{OH})\text{CH}_3$	2-propanol	isopropyl alcohol
	1,2-benzenediol	pyrocatechol (catechol)
$\text{CH}_3(\text{CH}_2)_3\text{CH}=\text{O}$	pentanal	<i>n</i> -valeraldehyde

TABLE 6-10. (Continued)

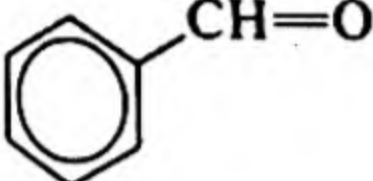
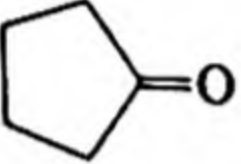

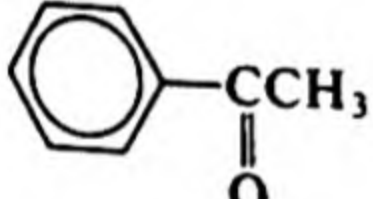
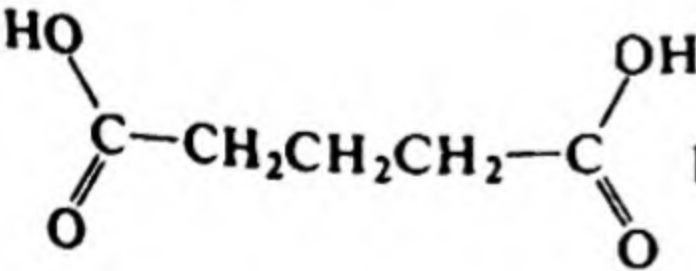
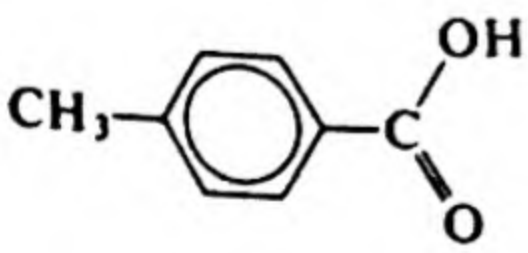
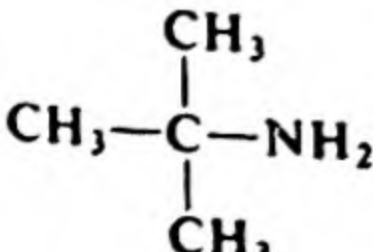
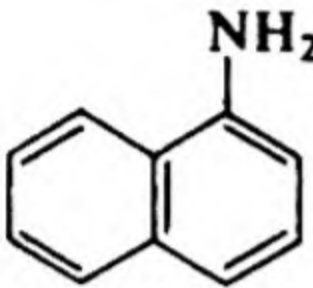
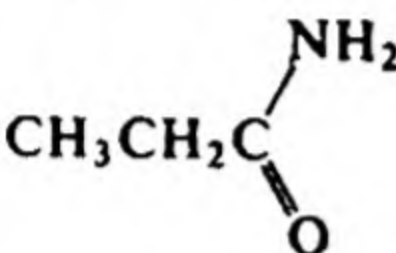
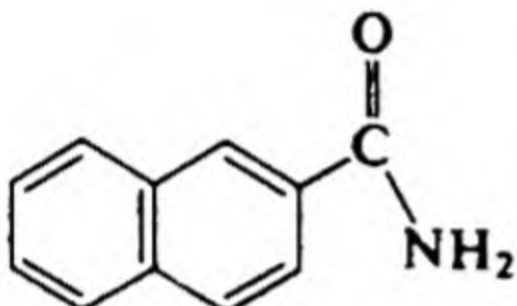
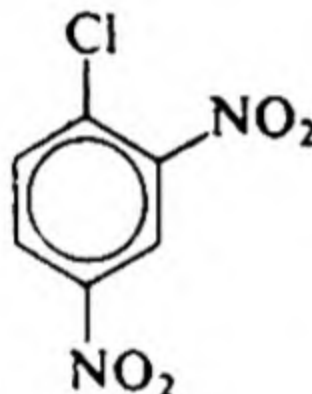
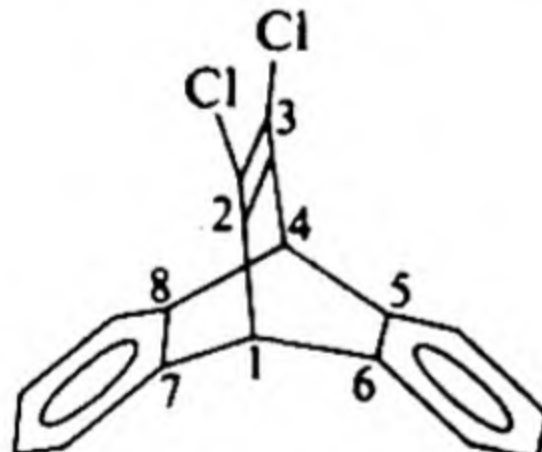
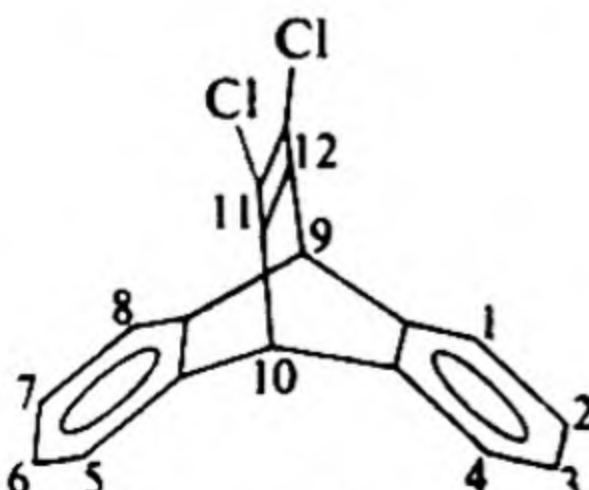
Structure	IUPAC Rules Name	Common Name
	benzenecarbaldehyde	benzaldehyde
$\text{CH}_3\text{CH}_2\text{C}(=\text{O})\text{CH}_2\text{CH}_3$	3-pentanone	diethyl ketone
	cyclopentanone	cyclopentanone
	1,4-dihydro-1,4-benzenedione; 2,5-cyclohexadiene-1,4-dione	benzoquinone* quinone ^{CA}
	1-phenylethanone	acetophenone
$\text{CH}_3\text{CH}(\text{CH}_3)\text{C}(=\text{O})\text{OH}$	2-methylpropanoic acid	isobutyric acid
	pentanedioic acid	glutaric acid
	4-methylbenzenecarboxylic acid	<i>p</i> -toluic acid
	1,1-dimethylethylamine	<i>t</i> -butylamine*

TABLE 6-10. (Continued)

Structure	IUPAC Rules Name	Common Name
	1-naphthylamine	α -naphthylamine
	propanamide	propionamide
	2-naphthalenecarbonamide	β -naphthoamide 2-naphthamide ^{CA}
	1-chloro-2,4-dinitrobenzene	2,4-dinitrochlorobenzene
$\text{CH}_2=\text{CH}-\text{CH}_2-\text{Cl}$	3-chloropropene	allyl chloride
	5,6;7,8-dibenzo-2,3-dichlorobicyclo[2.2.2]octatriene	
IUPAC numbering		
	11,12-dichloro-9,10-dihydro-9,10-ethenoanthracene ^{CA}	
CA numbering		

SUPPLEMENTARY READING

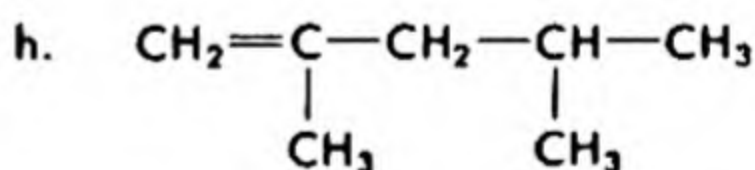
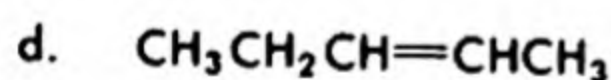
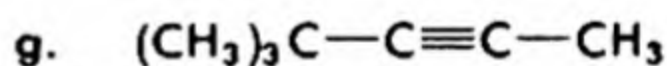
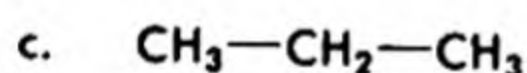
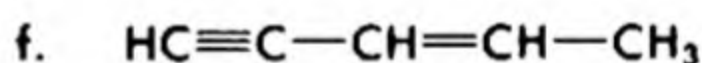
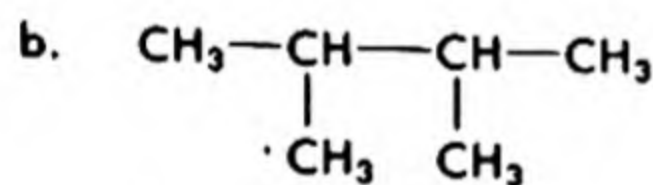
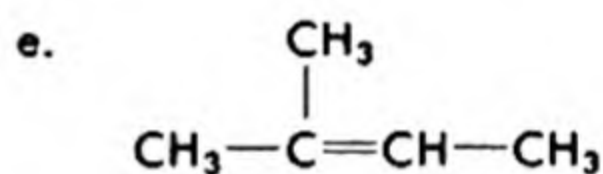
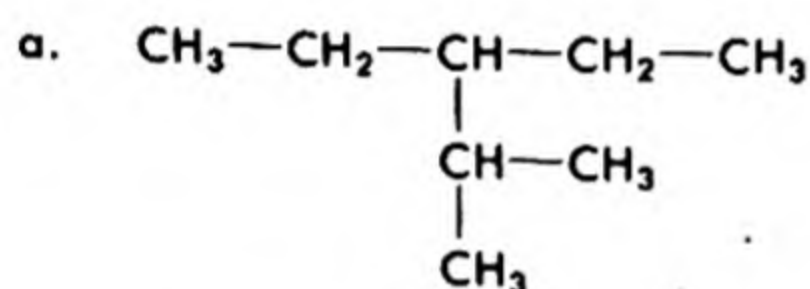
Hurd, C. D., "The General Philosophy of Organic Nomenclature," *J. Chem. Educ.*, **38**, 43-47 (1961).

QUESTIONS AND PROBLEMS

1. Write structural formulas for the following compounds and give their IUPAC names.

- | | |
|--------------------------------|-----------------------------|
| a. normal pentane | h. isohexane |
| b. isopentane | i. <i>n</i> -heptane |
| c. neopentane | j. isononane |
| d. ethyldimethylmethane | k. trimethylisobutylmethane |
| e. triethylmethane | l. 2°-butyl bromide |
| f. tetramethylmethane | m. isobutyl bromide |
| g. <i>sym</i> -diethylethylene | n. α -butylene |

2. Give the IUPAC names for the compounds which have the following structures:



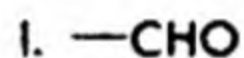
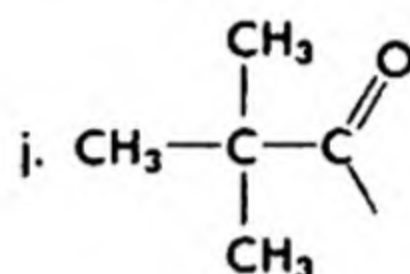
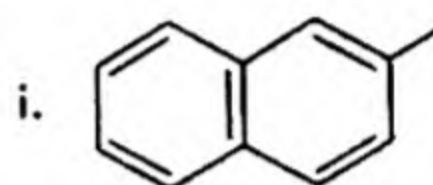
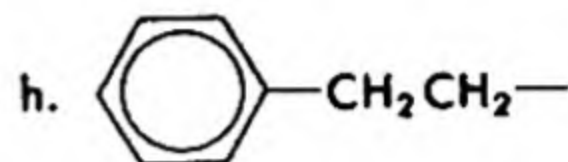
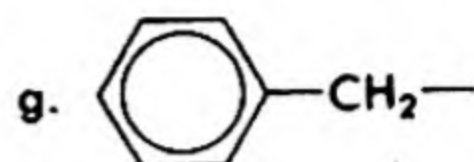
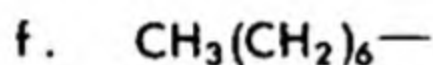
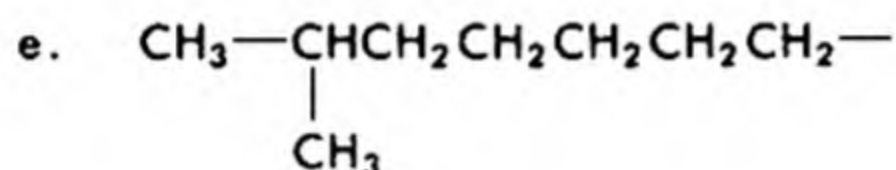
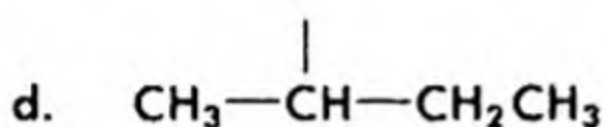
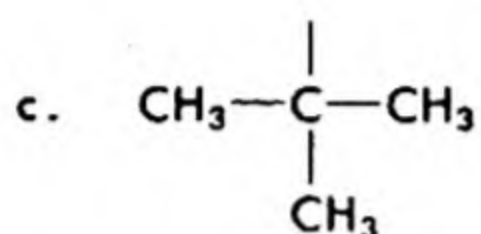
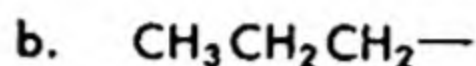
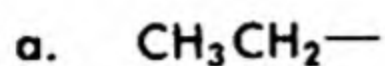
3. Write structural formulas for the following compounds.

- | | |
|---|----------------------------|
| a. 2,3-dimethylpentane | d. 3-methyl-2-pentene |
| b. 2,2,4-trimethyl-4-ethyl-3-isopropylheptane | e. 1,4-hexadiene |
| c. 2,2-dimethyl-6,6-diethyl-4-(1-methylethyl)octane | f. 3-propyl-1,4-pentadiyne |
| | g. 1-chloro-1,3-butadiene |
| | h. 3-iodo-3-methylpentane |

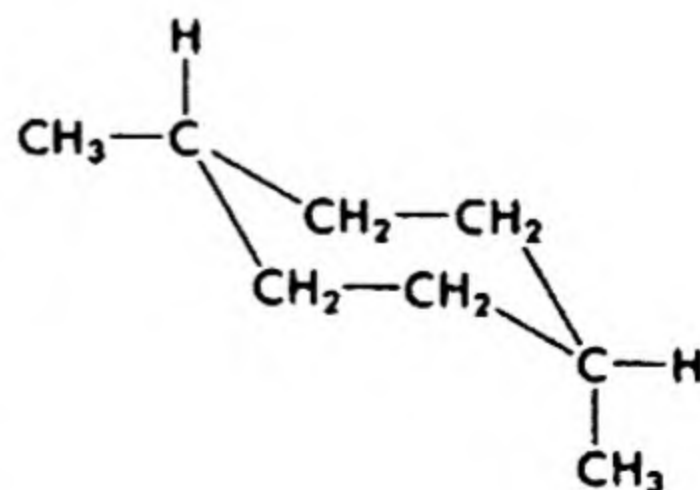
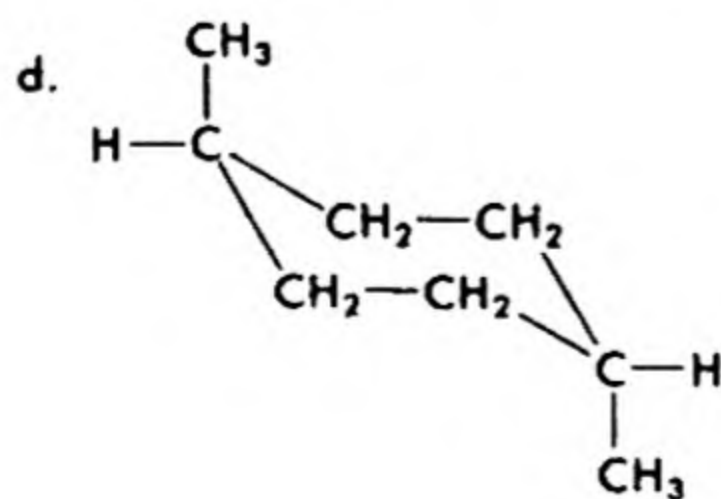
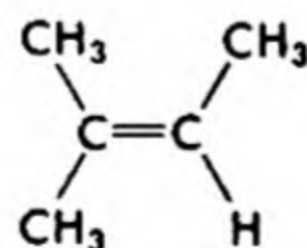
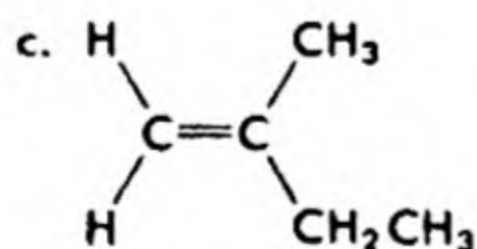
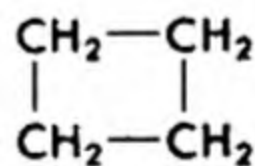
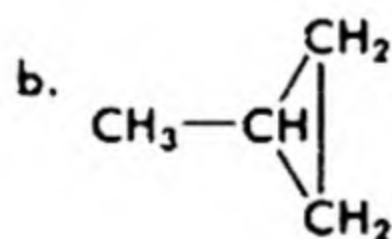
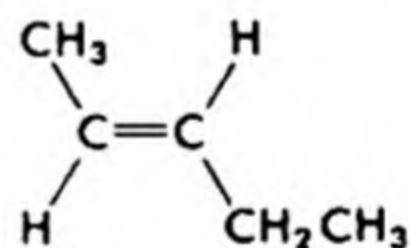
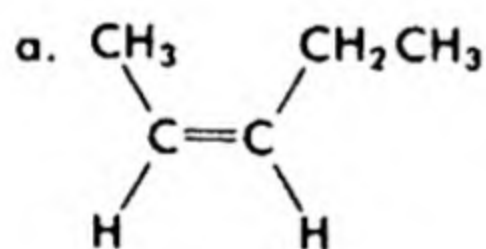
4. Judge whether each of the following IUPAC rules names is correct, and if not, write the correct name.

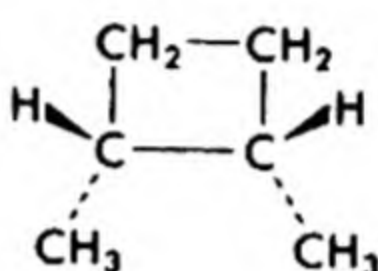
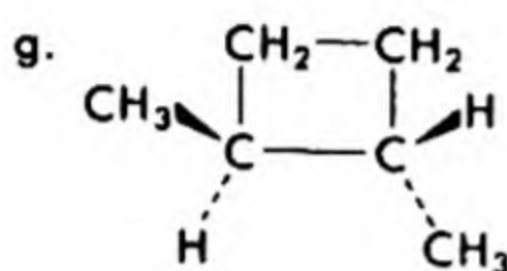
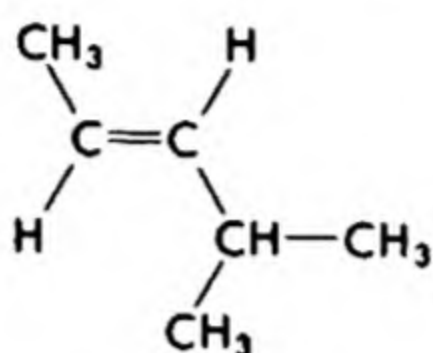
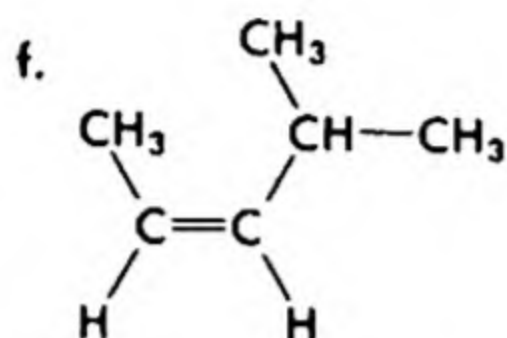
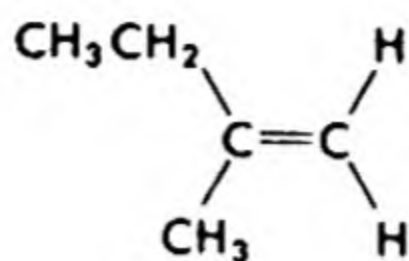
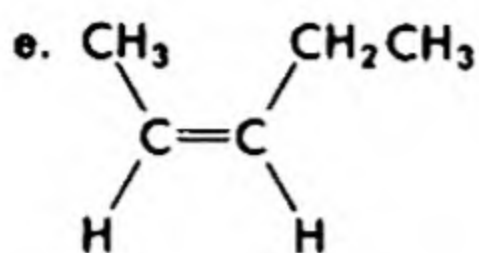
- | | |
|--------------------------|----------------------------------|
| a. 2-ethylbutane | e. 1-bromoethanoic acid |
| b. 2,3-dimethylbutane | f. β -bromopentanal |
| c. 2,4,4-trimethylhexane | g. diethylaminobenzene |
| d. 3-dimethylpentane | h. benzene-1,3-dicarboxylic acid |

5. Give the common and IUPAC rules names of the groups which have the following formulas.



6. Name the exact type of isomerism by which each of the following pairs of compounds is related. Write the full IUPAC name of each compound.





7. Write the structural formula and common name of an example of each of the following types of compounds.

a. a homolog of benzene

b. a polynuclear arene with isolated rings

c. a polynuclear arene with fused rings

8. Write the structural formulas for the following compounds, and point out the difference in structure between the compounds in each pair.

a. ethyl acetate, methyl ethyl ketone

b. methyl *n*-butyrate, *n*-butyl formate

c. methyl *n*-valerate, *n*-butyl acetate

d. ethanoic anhydride, ethyl ethanoate

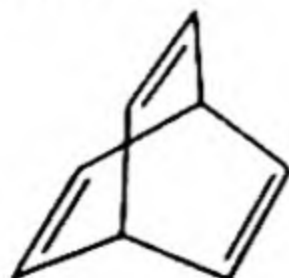
e. propionyl chloride, β -chloropropionic acid

f. *n*-butyryl chloride, *n*-butyl chloride

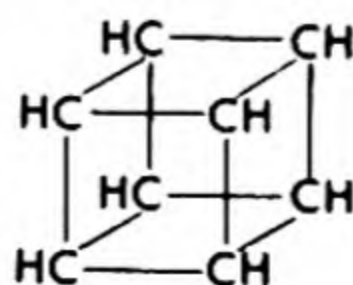
9. Illustrate with formulas the difference in the use of the terms, primary, secondary, and tertiary, as applied to classes of amines and as applied in names of amines.

10. Certain odd structures have appealed to the imagination of chemists, who have provided the following picturesque trivial names. Construct systematic names based on rules given in *The Ring Index*, Appendix 1-3.

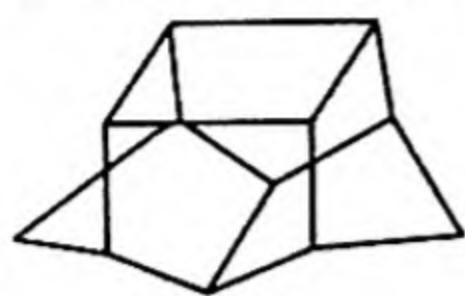
a. barrelene



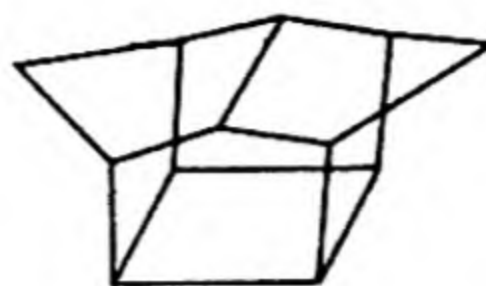
b. cubane



c. birdcage hydrocarbon



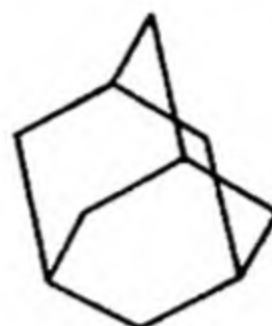
or



d. adamantane



or



7

Fundamental Chemical Properties

7-1 SINGLE BONDS

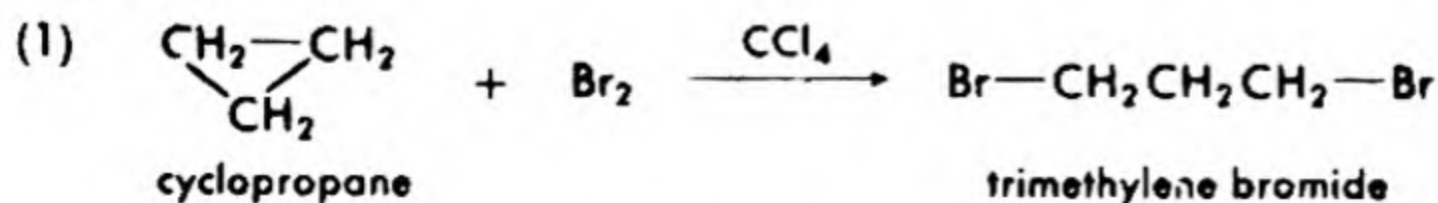
Fundamental differences in reaction pathways make reactions at single bonds generally differ considerably in rates from reactions at double or triple bonds. These pathways, or mechanisms, as they are called, are considered in later sections, after a sufficient body of factual material has been presented to make the implications of mechanism understandable. Even for now, however, it is convenient to consider reactions of singly bound atoms separately from those of multiply bound atoms.

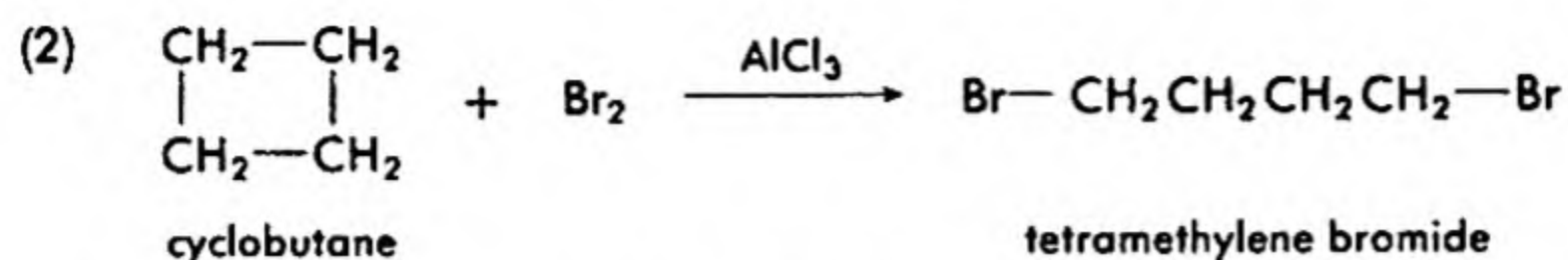
A. The Carbon-Carbon Bond

Of all the bonds in an organic molecule, a strain-free carbon-carbon single bond is least likely to be attacked under a wide variety of conditions. This is one factor which makes alkyl groups subordinate to functional groups in characterizing organic reactions. On the other hand, conditions under which carbon-carbon bonds can be attacked are neither uncommon nor difficult to achieve. Even a sort of musical chairs game, called *rearrangement*, can occur among parts of the carbon skeleton. But such reactions of carbon-carbon bonds most often accompany reactions at functional groups and usually require more powerful reagents or more drastic conditions in alkanes.

The inertness of the carbon chain is observed in the presence of such strong reagents as aqueous potassium permanganate, concentrated sulfuric acid, and concentrated nitric acid, none of which react appreciably with alkanes or medium- and large-ring cycloalkanes at temperatures below 50°.

Severe distortion of bonding orbitals, however, provides internal instability which makes carbon-carbon bond cleavage relatively easy. Thus, cyclopropane and cyclobutane rings are readily opened by strong reagents.





The reaction illustrated by eq. (1) occurs slowly at 20° in the absence of light or catalysts, but rapidly when Lewis acids (electron-pair acceptors) are added. The second reaction requires aluminum chloride at 20°, and still occurs slowly. Other substances which add to cyclopropane and, less readily if at all, to cyclobutane are hydrogen bromide, hydrogen iodide, and concentrated sulfuric acid. However, small rings are inert toward neutral permanganate solutions and ozone.

This reactivity, which is in marked contrast to the inertness of alkanes or larger-ring cycloalkanes under the same conditions, led Adolph von Baeyer to postulate the theory of strain in small rings (1890). Baeyer considered the reactivity of small rings to be a consequence of distortion of the normally 109.5° bond angles. Modern orbital and thermodynamic theories serve to substantiate and add detail to Baeyer's theory.

The bonds between ring carbon atoms are connected by σ MO's arising from overlap of p AO's, normally at 90° to each other (§4-1F), or of hybrid AO's with more or less s character up to sp^3 , normally at 109.5° to each other. The p AO's have better angular properties, but are poorer in lateral direction for σ MO's in small rings. The sp^3 AO's have poorer angles, but are better in lateral density concentration for overlap to form small-ring σ MO's. A hybrid orbital with less s character than sp^3 provides the best balance between the two factors (Fig. 7-1). The result, illustrated for cyclopropane in Fig. 7-1, gives bent σ orbitals in the ring with less stabilization by AO overlap than normal sp^3 -derived σ orbitals at 109.5°. The lower stabilization results in the internal potential energy or strain energy which is measured, for example, in a higher heat of combustion for cyclopropane than for the $\text{CH}_2\text{---CH}_2\text{---CH}_2$ portion of pentane.

B. Bonds to Hydrogen

(1) *Acidity.* In inorganic chemistry the hydrogen atom is frequently the hallmark of an acid. Indeed, it is true that any hydrogen-containing molecule or ion (even hydroxide ion!) may function as a proton-donor (Bronsted acid) under suitable conditions. But in practical experience, only compounds which are comparable to or better than water in proton-donating ability are classified as acidic. These are compounds in which hydrogen is attached to sixth or seventh period elements. A scale of acidity for X---H bonds is in the order $\text{X} = \text{F} > \text{OR} > \text{NR}_2 > \text{CR}_3$ and $\text{X} = \text{Cl} > \text{SR} > \text{PR}_2 > \text{SiR}_3$, when R represents hydrogen or hydrocarbon groups, or includes not more than one acyl group. In a periodic

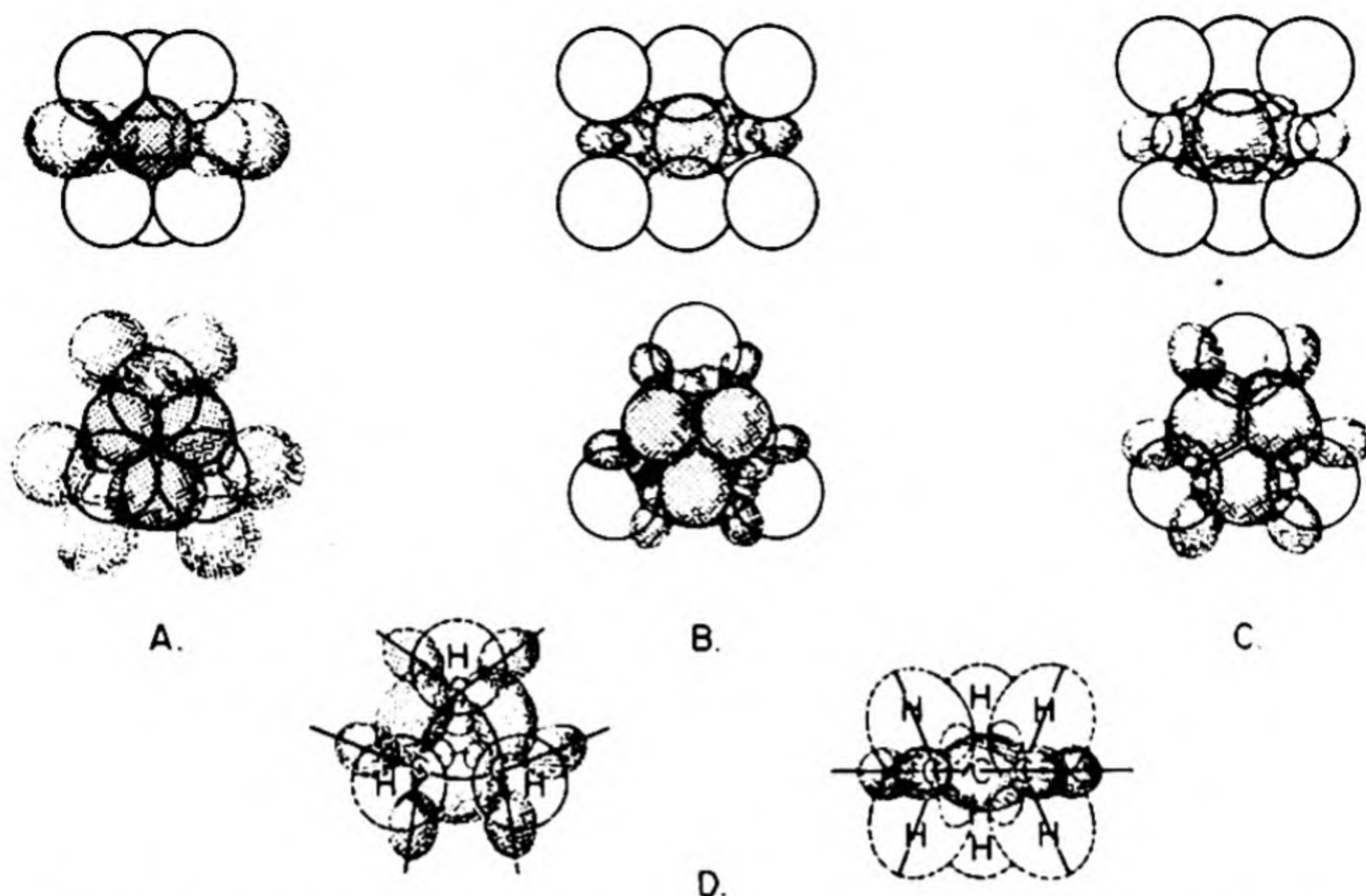
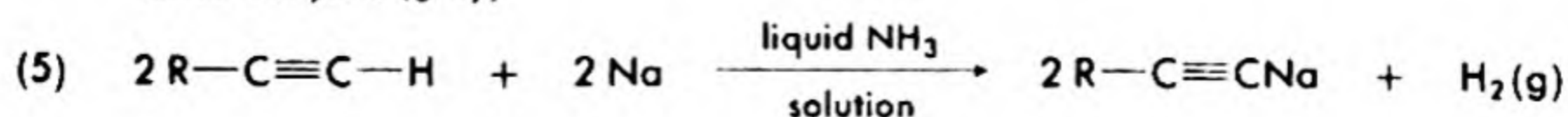
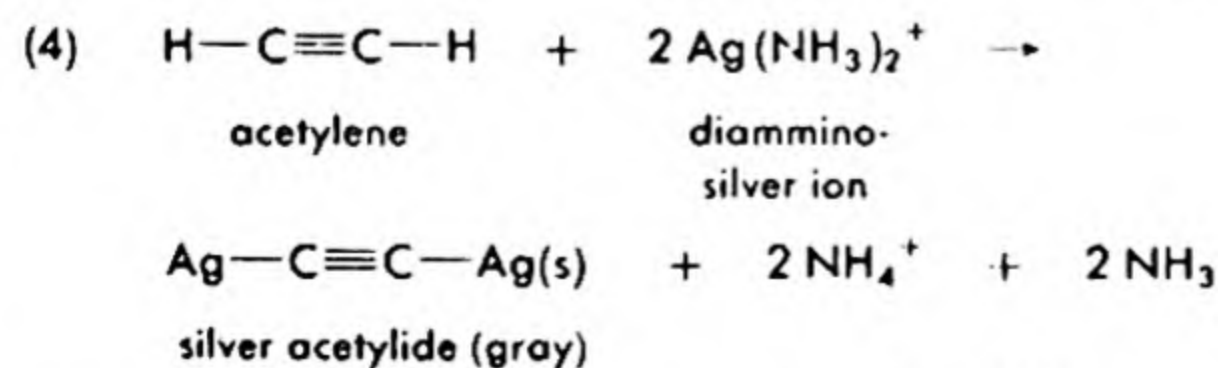
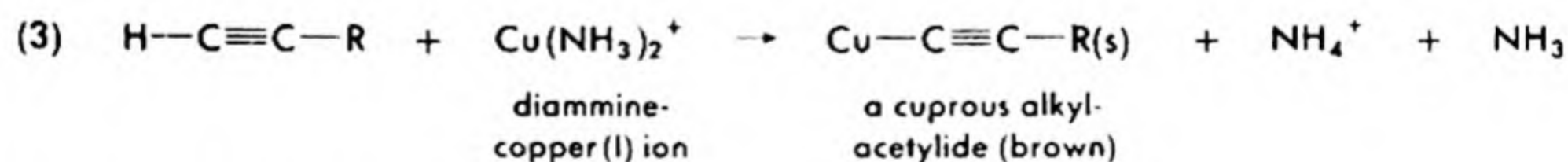


Fig. 7-1. Bond Hybridization in Cyclopropane. (A) Ring orbitals p only (no hybridization), outer orbitals $\frac{1}{2}s$, $\frac{1}{2}p$, (B) both ring and outer orbitals normal ($\frac{1}{4}s$, $\frac{3}{4}p$), (C) less hybridization than normal: halfway between A and B, (D) resultant molecular orbitals, with bent ring orbitals.

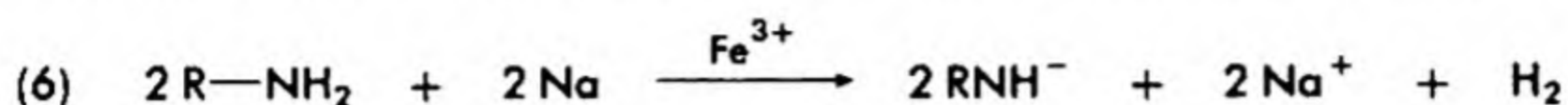
group, acidity increases with increasing period number; $\text{HX} = \text{HI} > \text{HBr} > \text{HCl} > \text{HF}$.

Most hydrocarbons show no measurable acidity in terms of reactions with common strong bases (e.g., sodium hydroxide), active metals (e.g., potassium), or protolytic solvents (e.g., water). That is, most hydrocarbons do *not* form salts with metals or metal hydroxides and do *not* provide hydronium ions in water.

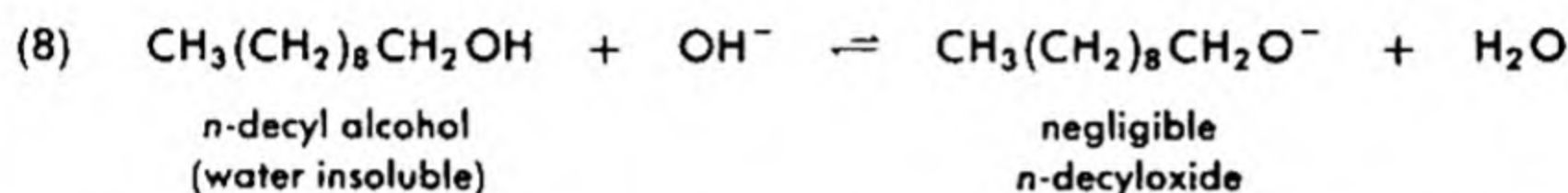
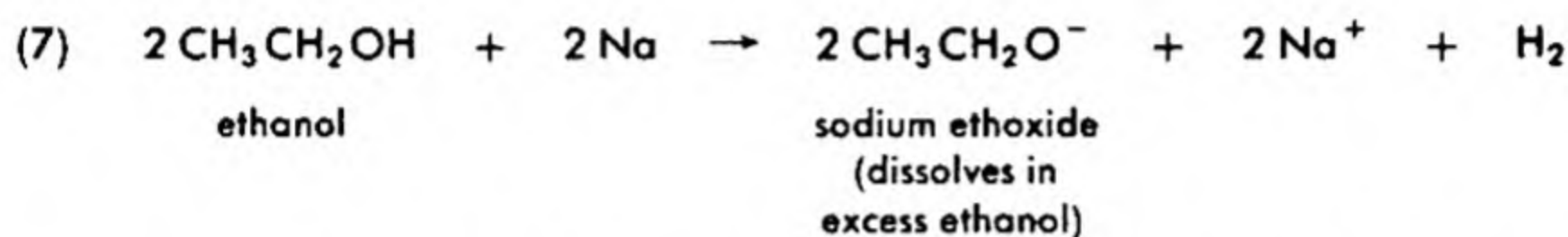
However, 1-alkynes do form metal salts because of the slight acidity characteristic of a carbon-hydrogen sp bond. (Compare hydrocyanic acid, $\text{H}-\text{C}\equiv\text{N}$.)



Primary and secondary amines are acidic enough to react sluggishly with some active metals, but not with common strong bases.

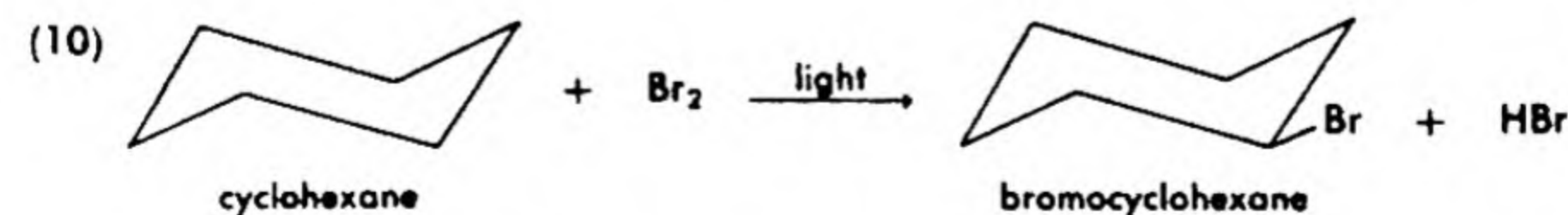
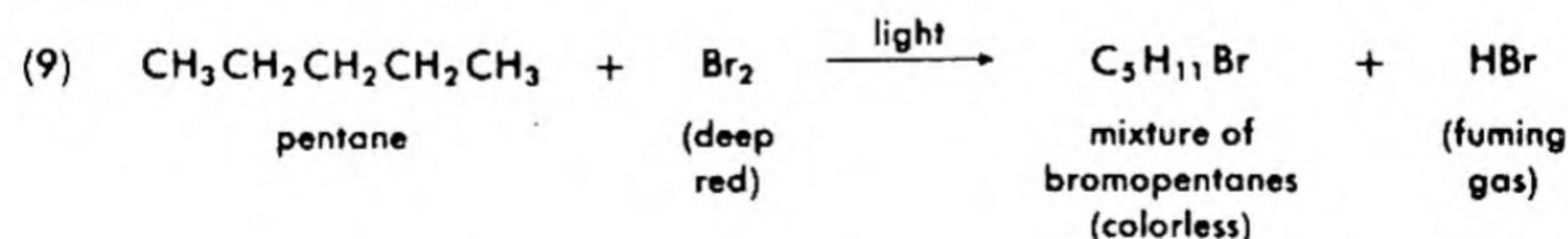


Alcohols react more vigorously toward active metals and equilibrate with sodium hydroxide. The latter reaction, however, is generally far from complete, and *cannot* be used to dissolve a water-insoluble alcohol by salt formation.



(2) *Substitution.* *Substitution* occurs readily at C—H and N—H bonds. In this reaction, electropositive hydrogen is displaced by an electronegative atom or group, especially halogen. (The term substitution has, since about 1930, been used also as a term equivalent to displacement, regardless of the nature of the groups involved.) The substitution in alkanes and unstrained cycloalkanes requires light or heat to promote reaction. Even then, the reaction is slow by comparison with the reactions of halogens with small-ring compounds and especially with unsaturated compounds (§7-2A). Bromine can be used to distinguish these three kinds of hydrocarbons by the rate and conditions under which it is decolorized. In the dark, alkanes and stable cycloalkanes fail to react at usual laboratory temperatures.

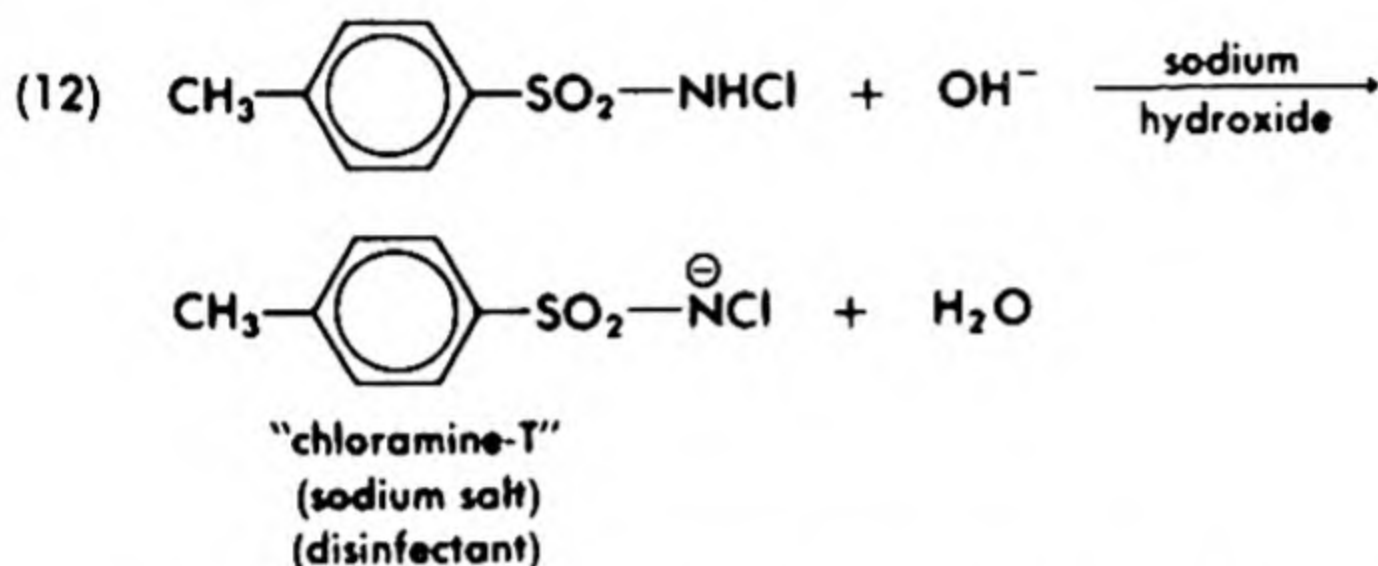
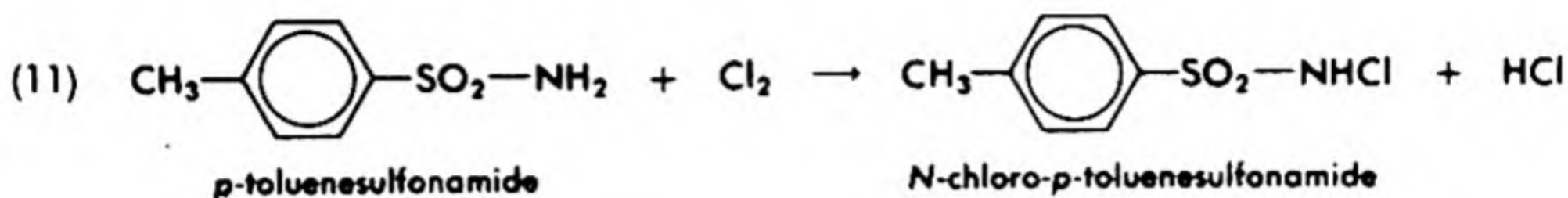
Light of short wavelengths promotes slow decolorization of the red bromine in alkanes.



Substitution can be demonstrated if the product hydrogen halide is evolved from an inert solvent such as carbon tetrachloride and held in the reaction vessel until concentration sufficient to form fumes has built up.

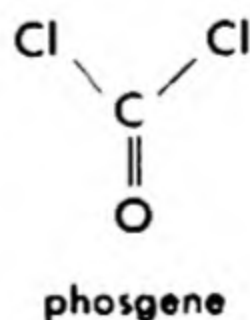
Lack of fumes in moist air may indicate an addition reaction or failure to observe hydrogen bromide in a substitution.

Nitrogen atoms can also be substituted, often more easily than carbon atoms in the same compound.

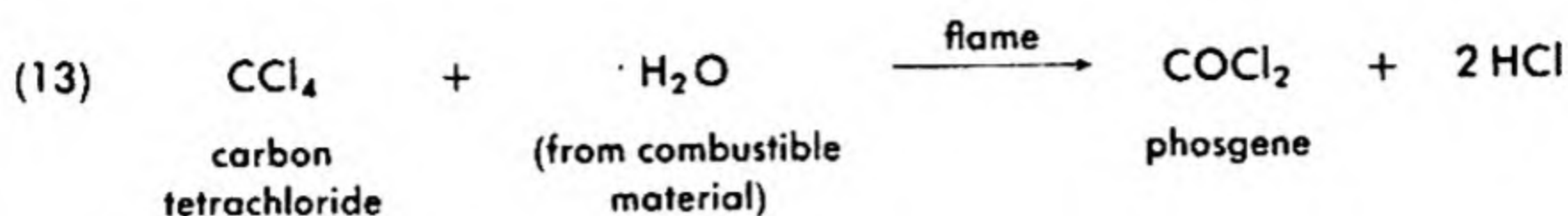


(3) *Combustion.* Hydrocarbons and their derivatives which still contain hydrogen are active reducing agents when hot (temperatures above 500°). Alkanes can react explosively with oxygen and chlorine. A significant portion of the power that runs industrial machinery, and most of that which runs the present transportation system, are supplied by combustion of petroleum fractions, in large part alkanes. Volatile organic compounds present a fire and explosion hazard wherever they are handled. Adequate precautions in ventilation, trapping of systems, and avoidance of flames or hot wires in the vicinity of open vessels of organic compounds are necessary for personal and property protection.

Complete combustion of organic compounds gives carbon dioxide and water, along with oxides of other oxidizable elements. Nitrogen may form oxides or the gaseous element. Halogens often appear in carbonyl halides, such as phosgene, which is a poison, hence may add to the hazard of fire fighting. Incomplete combustion may also produce a variety of toxic substances, such as carbon monoxide.



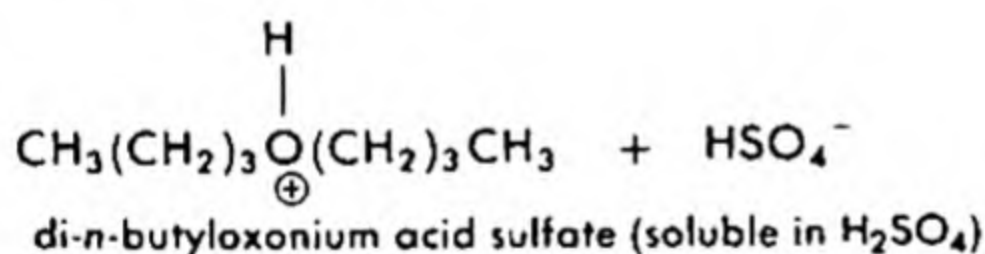
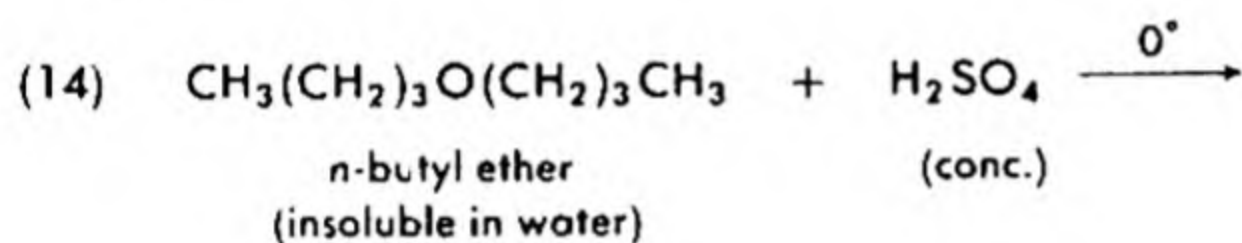
Highly halogenated compounds are, in general, noncombustible, although they can be decomposed in flames supported by combustible materials. Use of carbon tetrachloride as a fire extinguisher has been discouraged by fire marshals for this reason.



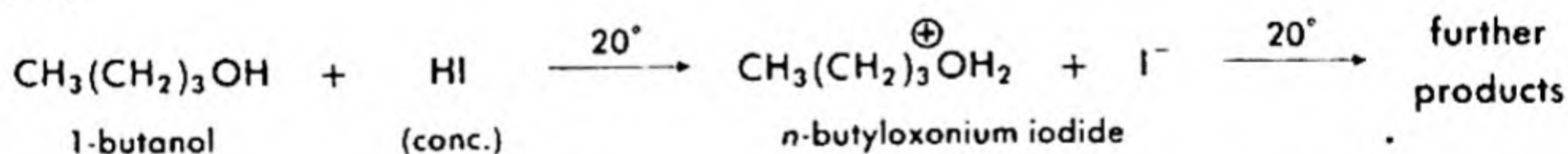
C. Unshared Electron Pairs

Any compound with an atom that has an unshared pair of electrons is a potential proton acceptor (Brønsted base) and may, under suitable conditions, form a bond to a hydrogen ion (proton). Again, as with the counterpart acids, compounds vary widely in their ability to function. Basicity in the series of compounds R_nX varies in the order $\text{X} = \text{N} > \text{O} > \text{F}$, $\text{X} = \text{P} > \text{S} > \text{Cl}$ when R is hydrogen or an alkyl group. Basicity decreases down a periodic group with increasing period number; $\text{X} = \text{O} > \text{S} > \text{Se}$. A negative charge greatly increases basicity; $\text{:}\ddot{\text{O}}\text{H}^-$ is much stronger than $\text{H}_2\ddot{\text{O}}$, for example.

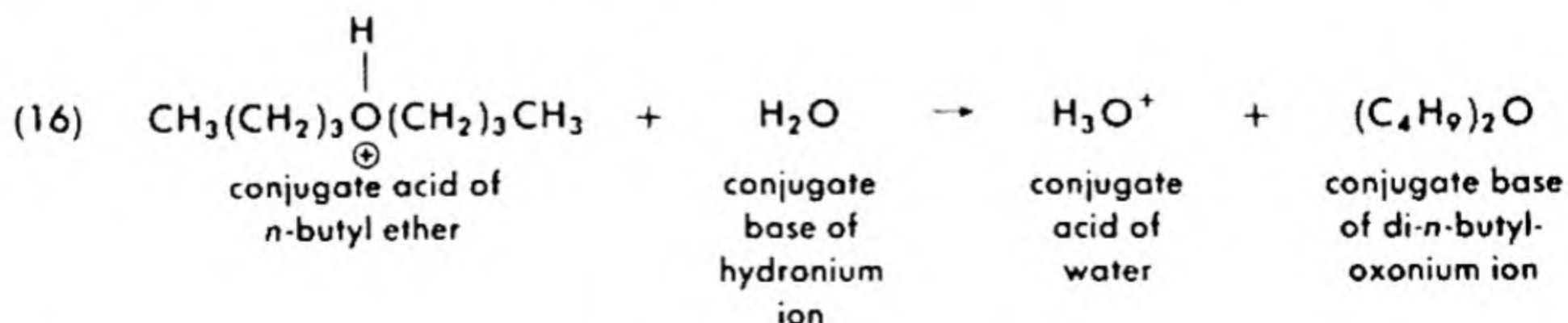
In practice, halides are not considered to be basic (even halide ions react only with strong acids, for example, H_2SO_4). Alcohols and ethers are weak bases which can be dissolved in strong acids (such as concentrated sulfuric acid) by salt formation even when they are insoluble in water.



(15)

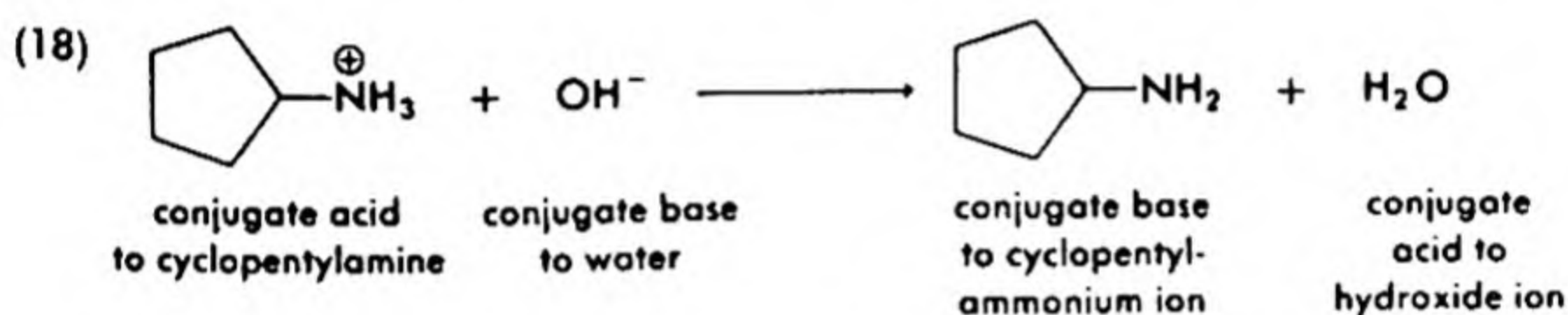
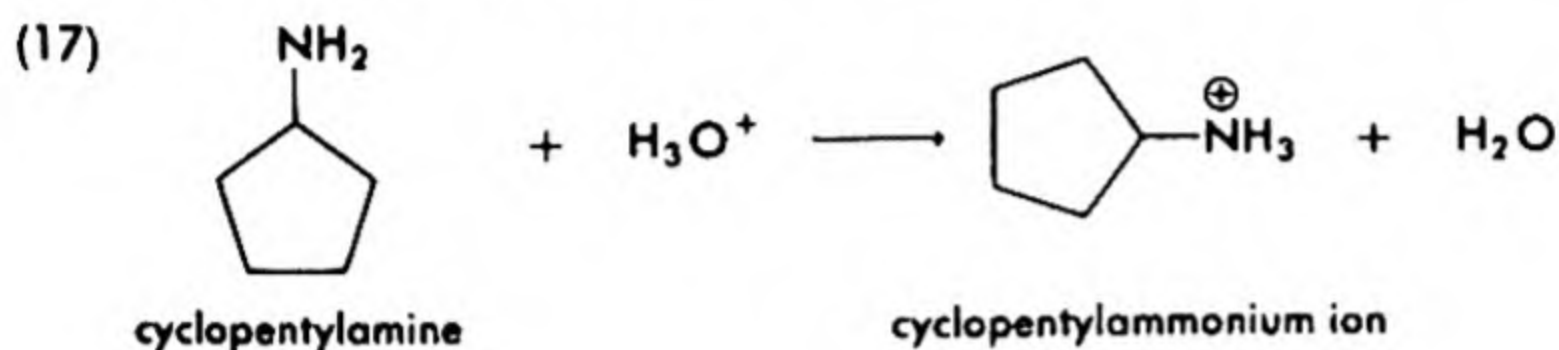


An insoluble ether can be recovered from cold sulfuric acid solution by dilution of the acid with water.

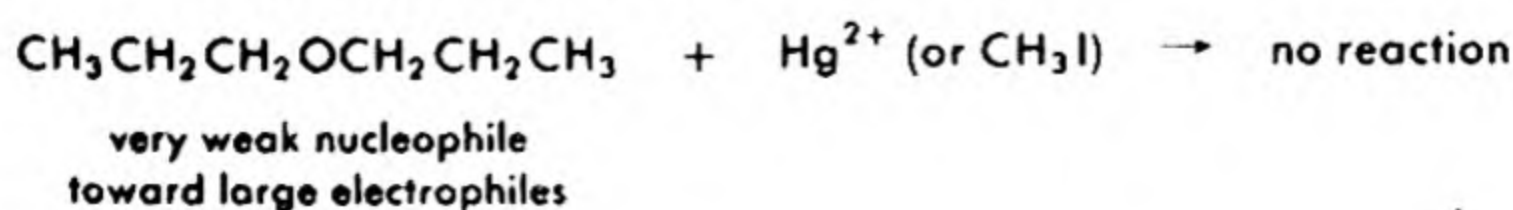
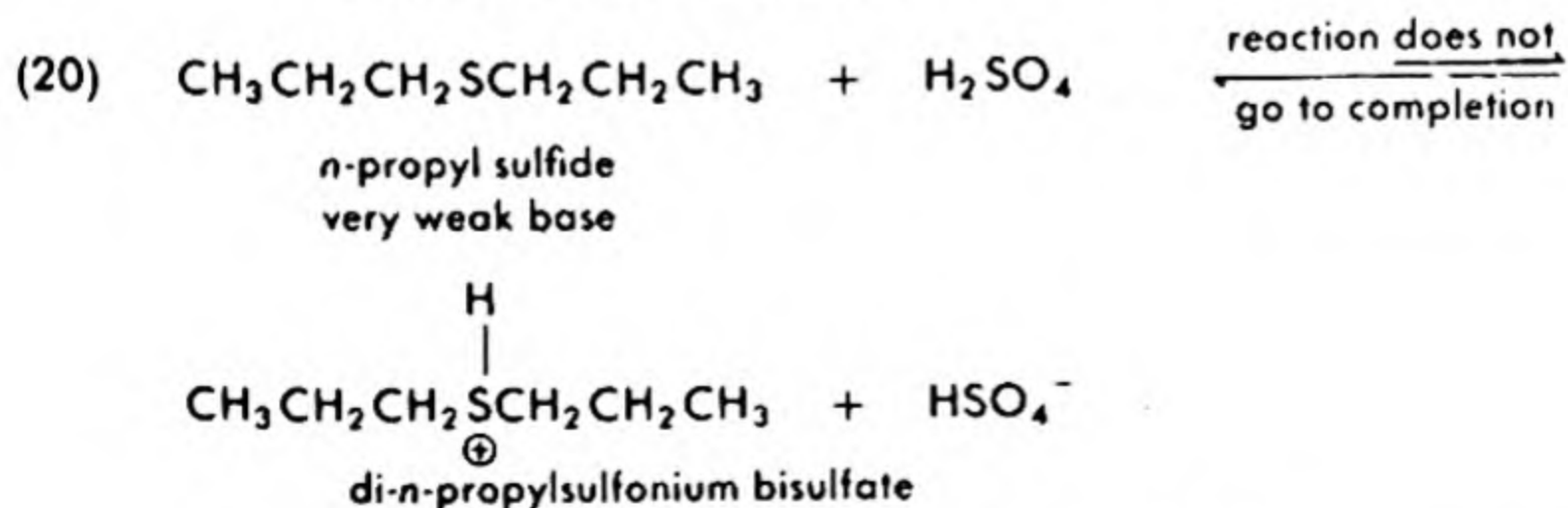
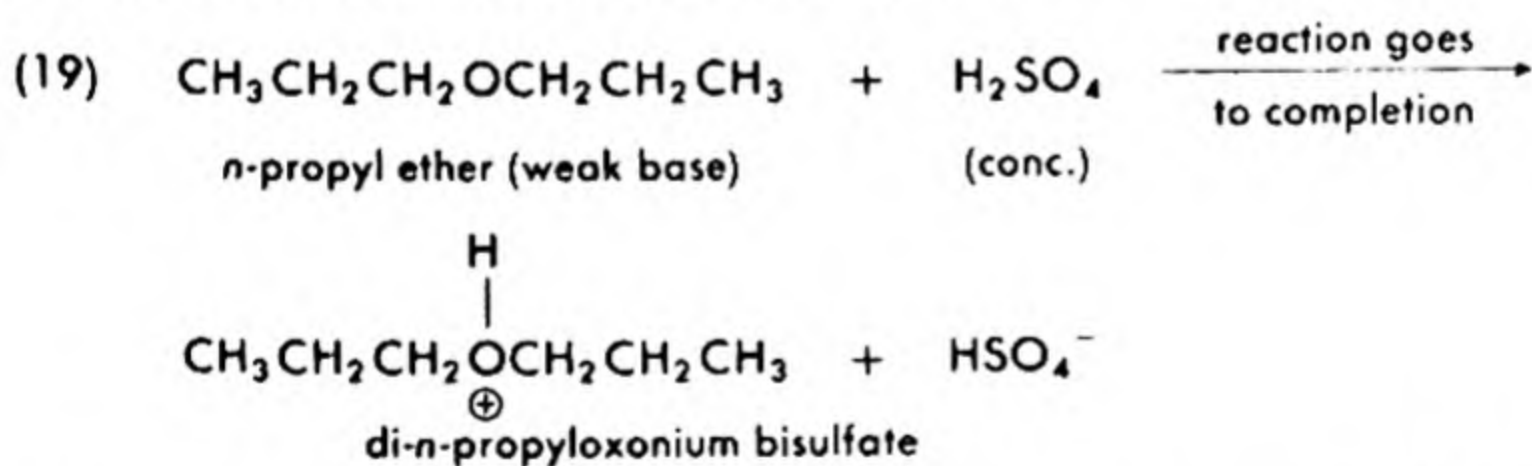


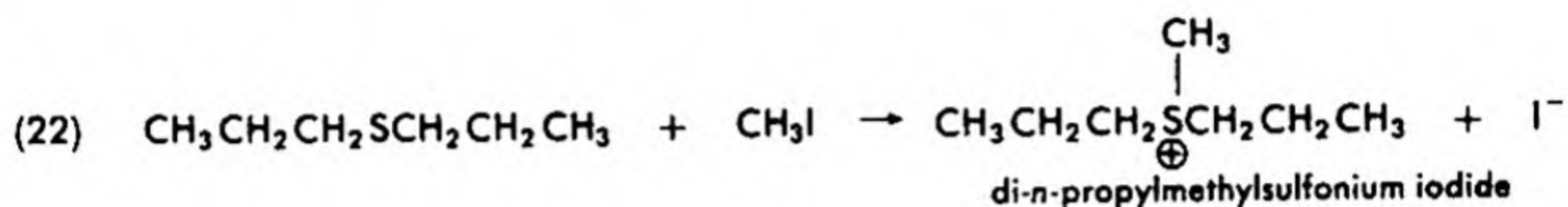
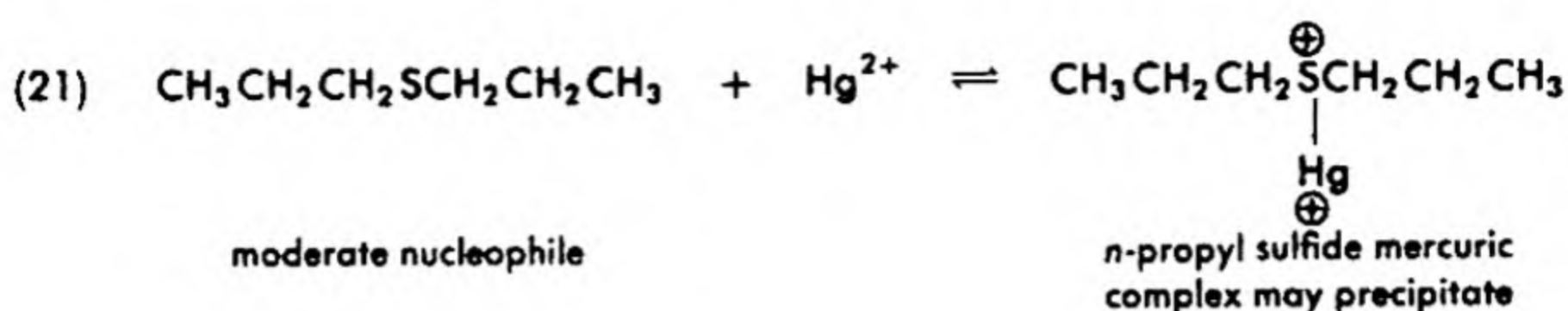
In Brønsted nomenclature, the acid and base related by transfer of one proton are conjugate to each other, as indicated in eq. (16).

Most amines are basic enough to react with dilute acid solutions; amines are, therefore, considered a basic class of compounds. However, notable exceptions occur (§7-3A(3)). Alkylamines are slightly stronger bases than ammonia. In general, amines dissolve by salt formation in water and are recoverable by treatment of the salt solutions with a stronger base, such as sodium hydroxide.

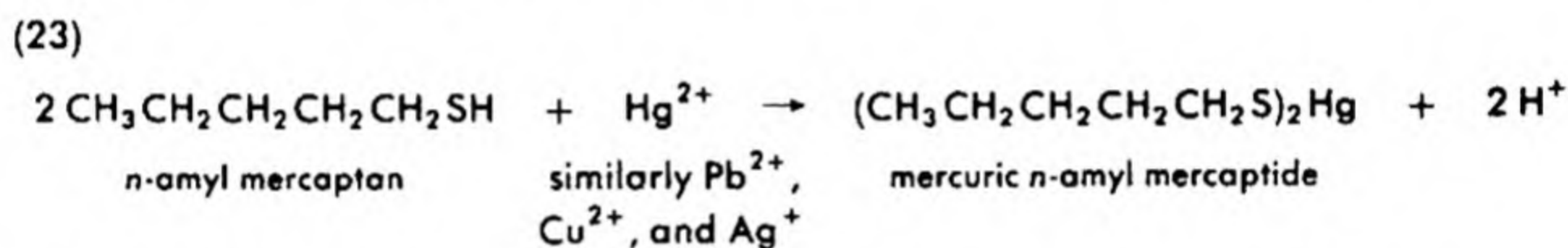


Unshared electron pairs may react with electron seekers (*electrophiles*) other than protons. In the general role of electron donors, unshared electron pair-containing molecules are called *nucleophiles*. Electrophiles other than protons may have different orders of reactivities toward nucleophiles. A case in point is the marked contrast between relative reactivities of ethers and sulfides toward protons and toward such electrophiles as heavy metal ions or alkyl halides.





The nucleophilic character of divalent sulfur is amply demonstrated in mercaptans (the name is a contraction of mercurium captans, taking mercury). These compounds precipitate heavy metal ions in much the same manner that hydrogen sulfide does.

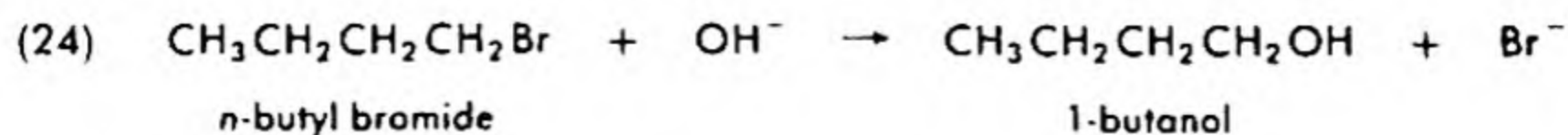


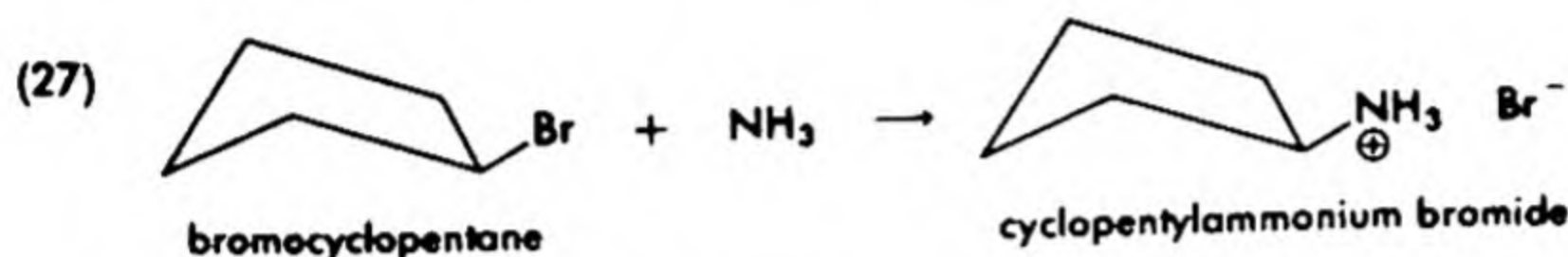
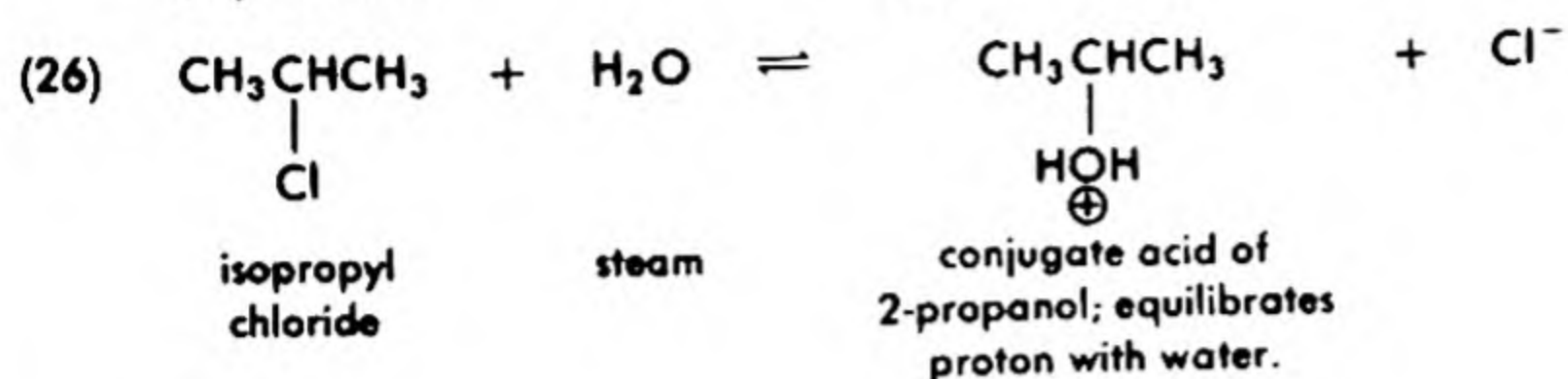
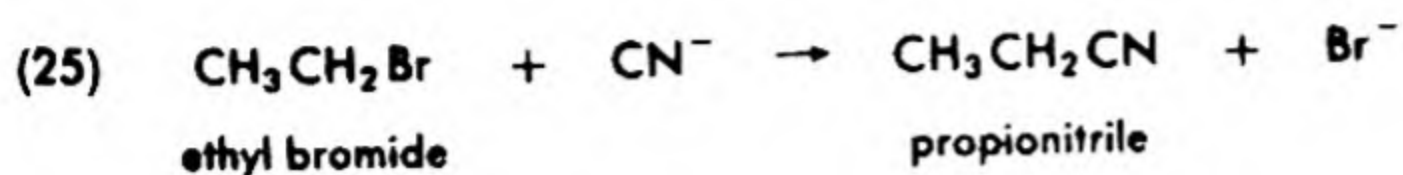
D. Carbon-Halogen, Carbon-Oxygen, and Carbon-Nitrogen Bonds

A common type of reaction involving a carbon-heteroatom bond (heteroatom = atom other than carbon) is a displacement. Either of two factors is important in such displacements: the polarity of the bond, or the ease with which the bond breaks to form ions. Whereas groups on the carbon atom may influence these factors in opposite directions, the nature of the heteroatom generally has the same effect on polarity and ease of ionization of the compound. Both are increased by increasing electronegativity differences between the carbon atom and the heteroatom. Consequently, the ease of displacements increases in the order $\text{C}-\text{N} < \text{C}-\text{O} < \text{C}-\text{X}$ in which X is a halogen other than fluorine. Fluorine is anomalous in saturated compounds because its strong binding energy to carbon offsets the polarity effect. When bond-breaking is less influential in the pathway of the reaction than bond-making, fluorine, like other halogens, is a readily displaceable group.

It follows, then, that uncatalyzed displacements of $\text{R}-\text{Cl}$, $\text{R}-\text{Br}$, and $\text{R}-\text{I}$ generally occur readily; those of ROH and ROR are difficult, if they occur at all, and those of RNH_2 and similar species are almost never seen.

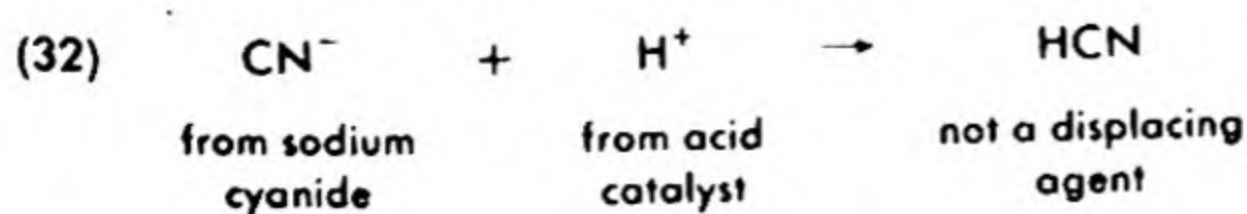
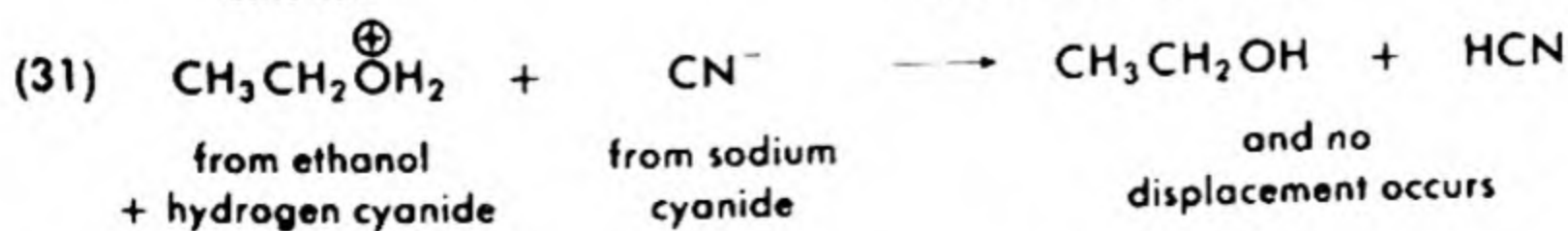
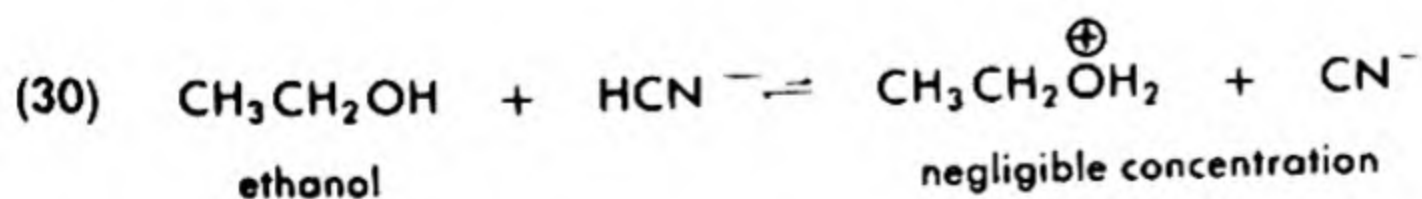
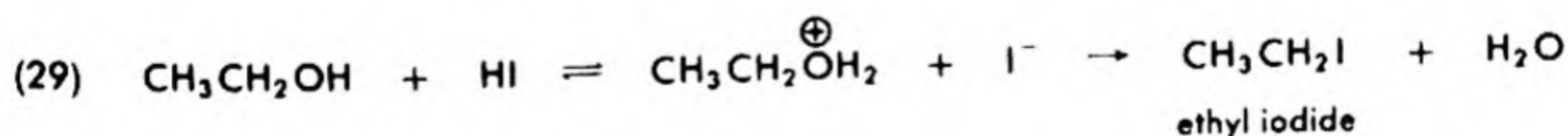
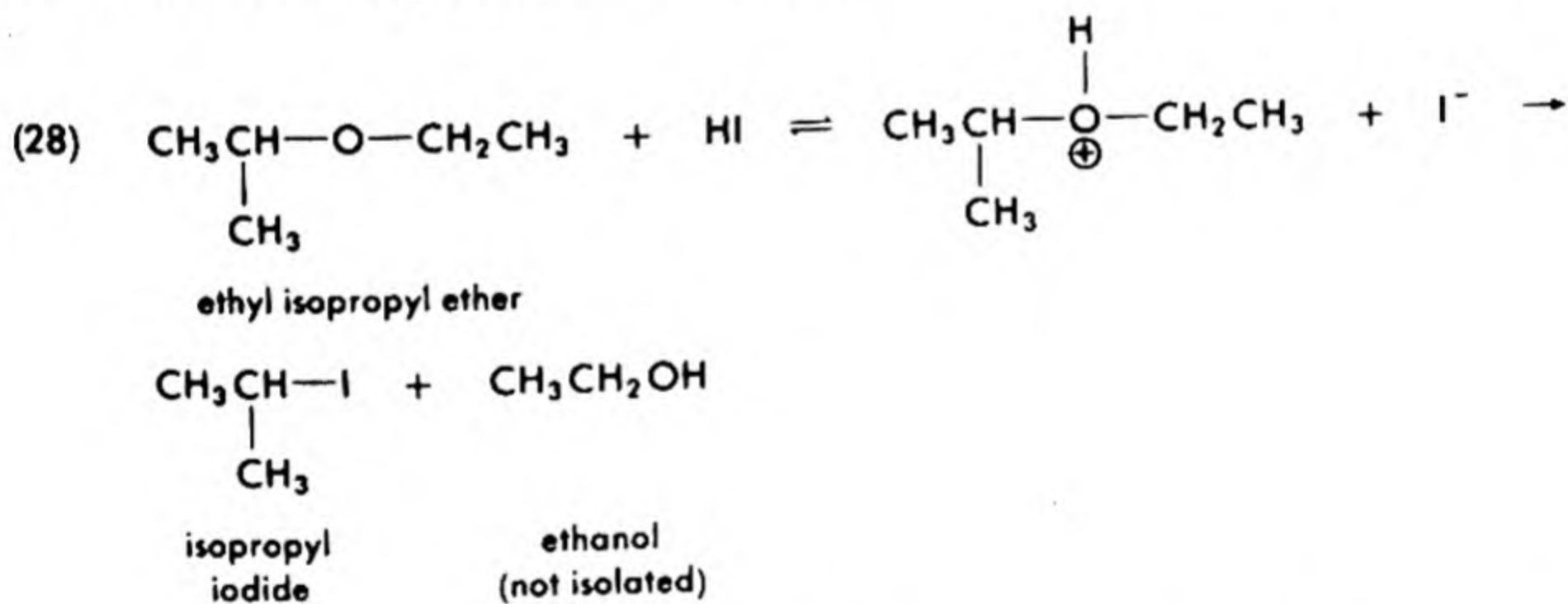
Any basic anion or basic molecule serves to displace the heavier halogens. See also §5-2A, eq. (16).

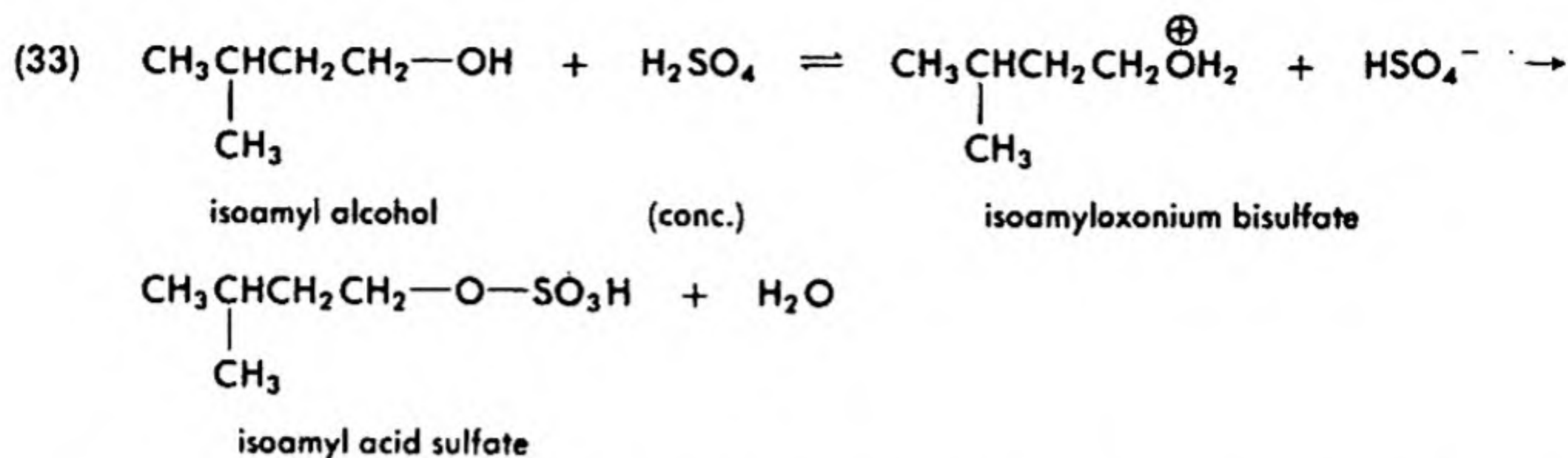




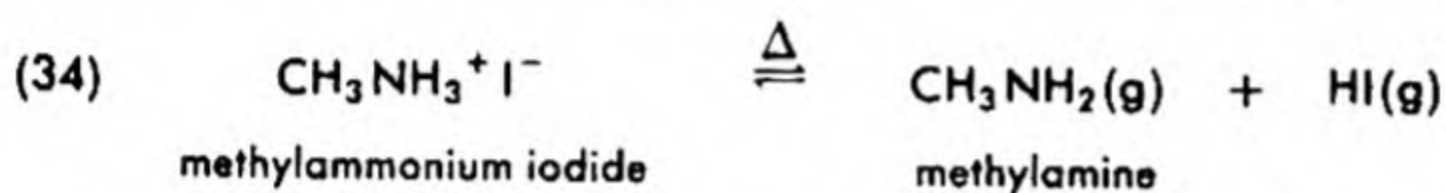
Alcohols and ethers fail to react under these conditions.

The electronegativity difference between carbon and a heteroatom is greatly increased when the heteroatom is protonated. Thus, the conjugate acids of alcohols and ethers readily undergo displacements. However, if the displacing nucleophiles are not to nullify the effect of acid catalysis by reacting with protons from the catalytic acid or the oxonium ions, they must be very weak bases. Eqs. (28) through (33) illustrate some practicable and some impracticable displacements.

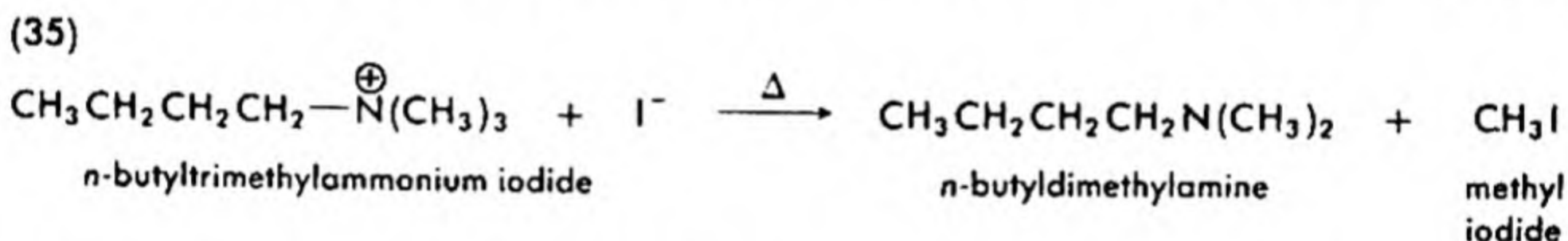




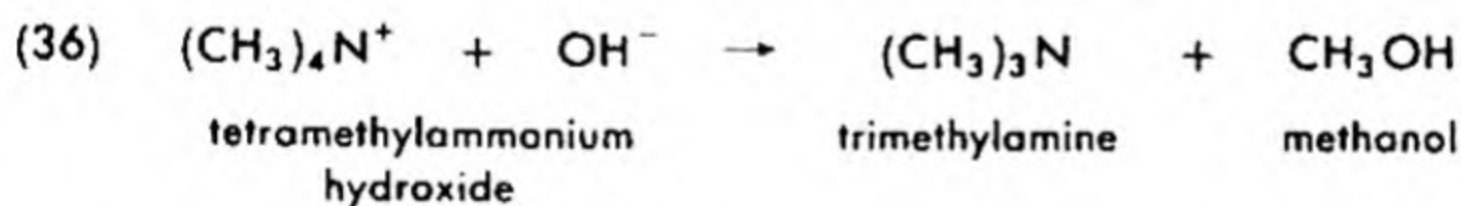
Even acid catalysis is insufficient to promote displacements involving cleavage of a carbon-nitrogen bond. Higher temperatures are required, under which circumstances ammonium salts often decompose into the related amines and acids before displacement can occur.



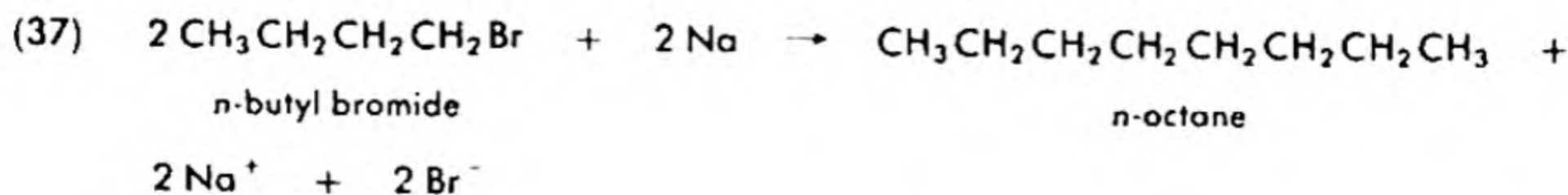
However, quaternary ammonium salts have no nitrogen-hydrogen bond to provide such an acid-base cleavage, and displacement becomes the sole

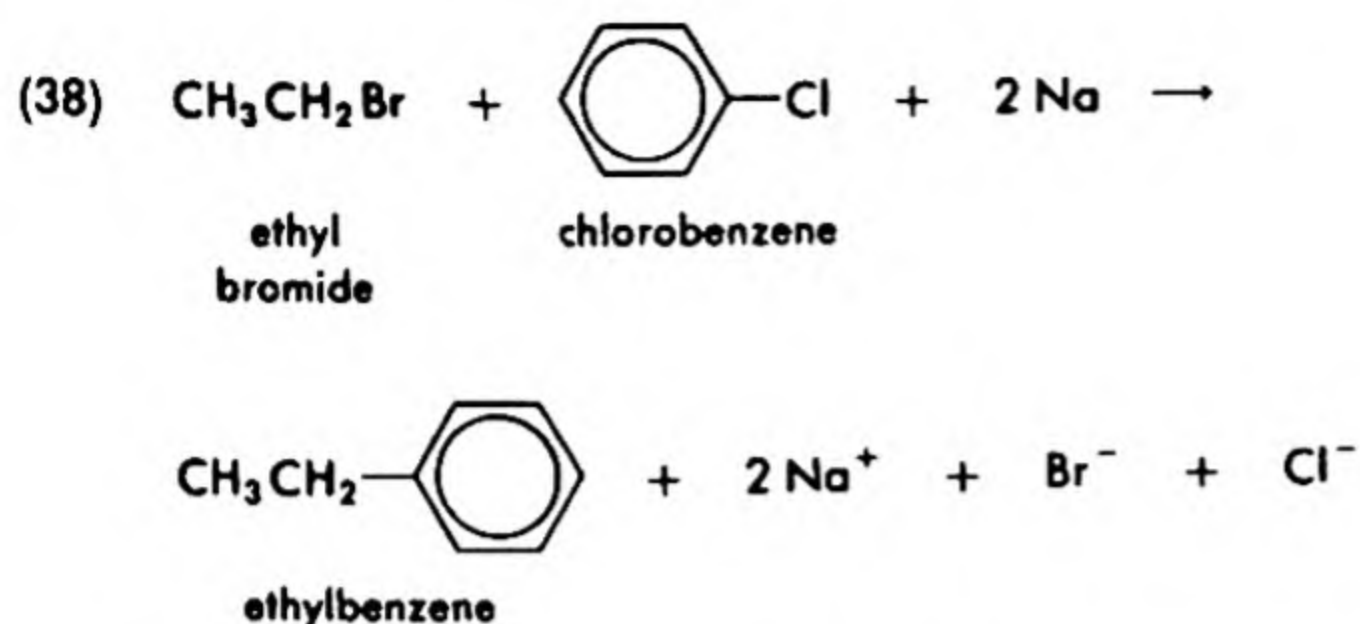


alternative. Displacement of *n*-butyltrimethylammonio group by iodide is an example of a general reaction. Displacement of a trimethylammonio group by hydroxide ion is *not* practicable in higher tetraalkylammonium hydroxides as a different reaction then occurs (see eq. 43).



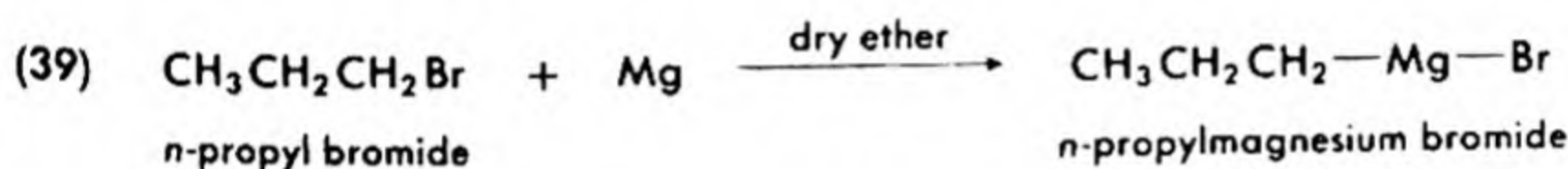
The high polarity of carbon-halogen bonds is responsible for another kind of displacement reaction which involves an active metal. Corresponding reactions of ethers and tertiary amines do not occur except under the most extreme conditions; it may be recalled that alcohols and, to some extent, primary and secondary amines undergo hydrogen displacement with active metals (§7-1A(1)). Alkyl halides and mixtures of alkyl and aryl halides react with sodium or potassium to form, among various by-products, hydrocarbons from the combined groups.





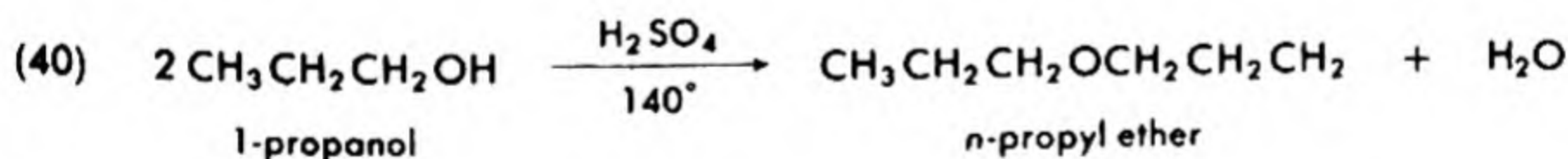
Although this reaction, called the Wurtz reaction, now has limited utility, it served at one time for the preparation of symmetrically substituted even alkanes and for structural confirmation of such alkanes.

Active metals form organometallic compounds, in which a metal atom is covalently bound to a carbon atom. The *Grignard reaction*, eq. (39), is most useful and quite general. Both alkyl and aryl halides give good yields of product under suitable conditions. The reaction is discussed in more detail in §19-2A.

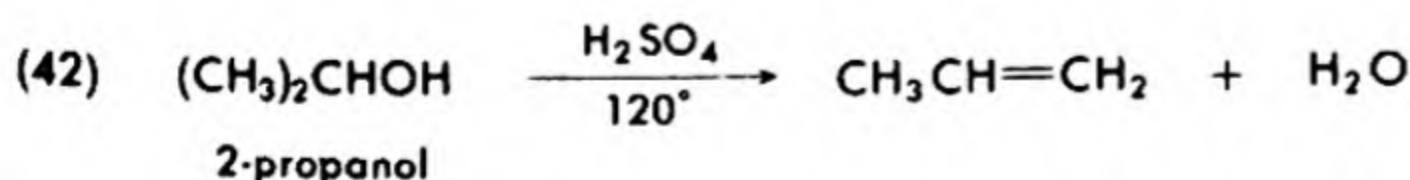
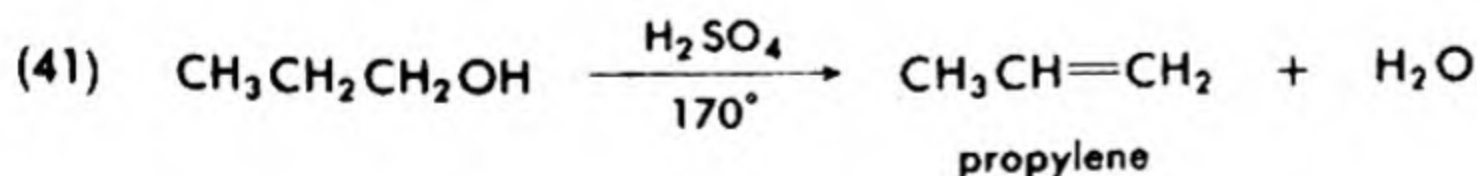


Another common reaction involving carbon-heteroatom bonds is elimination. This reaction often competes with displacement, and is favored generally by more drastic conditions (higher temperatures, more basic reagents). Secondary and tertiary compounds are especially susceptible to elimination.

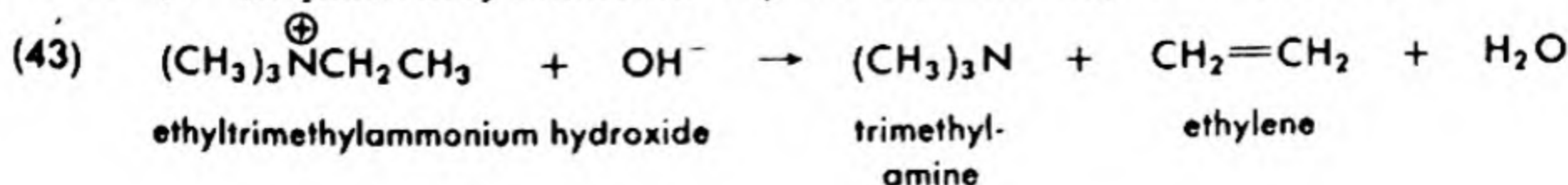
Displacement:



Elimination:



General for all quaternary ammonium hydroxides with higher alkyl groups:



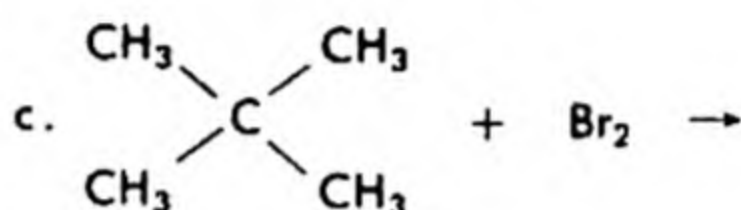
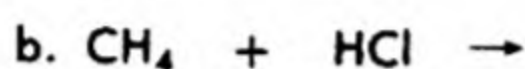
SUPPLEMENTARY READINGS

Herz, W., *The Shape of Carbon Compounds*, Benjamin, New York, 1963, Chapter V.

VanderWerf, C. A., *Acids, Bases and the Chemistry of the Covalent Bond*, Reinhold, New York, 1961, Chapters 1 and 2.

QUESTIONS AND PROBLEMS

1. Write equations for those of the following implied reactions which occur, including conditions. If the compounds do not react under mild conditions, write NR.



2. What is a strained ring? Why are large rings not strained? What does ring strain show about the valence bonds on a carbon atom?

3. Can cycloalkanes with five or more atoms in the ring be distinguished chemically from alkanes? Why?

4. Write equations for any reactions that occur in the following mixtures of substances under moderate conditions. Use structural formulas. Indicate essential special conditions. If no reaction occurs, write the formulas of the reagents and NR.

- | | |
|---|---|
| a. 1,2,3-trimethylcyclopropane +
bromine in carbon tetrachloride | i. 2°-butyl chloride + ammonia |
| b. 1,3-dimethylcyclobutane + bro-
mine in carbon tetrachloride | j. ethyl alcohol + hydrochloric
acid |
| c. cyclopentane + bromine in car-
bon tetrachloride | k. methyl alcohol + sodium hy-
droxide |
| d. 1,2,3-trimethylcyclopropane +
hydrogen iodide | l. diethylcarbinol + sodium |
| e. <i>trans</i> -1,2-dimethylcyclohexane
+ hydrogen iodide | m. sodium ethoxide + <i>sec</i> -butyl
bromide |
| f. ethyl bromide + sodium sulfide | n. <i>n</i> -butylamine + ammonia |
| g. methyl iodide + water | o. diethylammonium chloride +
dilute sodium hydroxide |
| h. isobutyl chloride + sodium cy-
anide | p. tetramethylammonium bisulfate
+ dilute barium hydroxide |

5. Each compound to be prepared, a–n, can be made in one step from the suggested starting material and inorganic reagents. Write equations for the required reactions, including necessary special conditions. Use structural formulas for organic compounds.

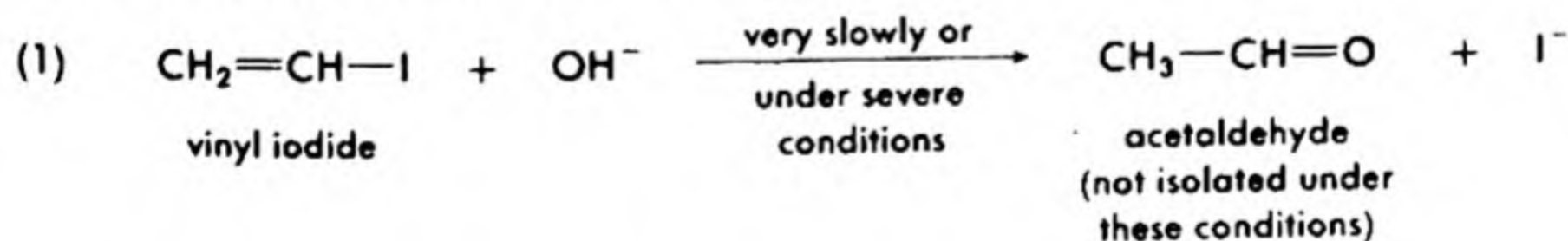
- | | |
|---|--|
| a . methyl chloride from methane | i . <i>n</i> -propyl ether from the suitable alcohol |
| b . ethyl chloride from an alkane | j . <i>n</i> -amyl mercaptan from the suitable bromide |
| c . bromocyclohexane from cyclohexane | k . isoamyl sulfide from the suitable bromide |
| d . <i>n</i> -propyl alcohol from <i>n</i> -propyl bromide | l . triethylamine from ethyl bromide |
| e . isoamyl cyanide from a suitable halide | m . trimethylammonium iodide from trimethylamine |
| f . potassium <i>t</i> -butoxide from <i>t</i> -butyl alcohol | n . tetraethylammonium bromide from a tertiary amine and an alkyl halide |
| g . <i>n</i> -amyl bromide from the suitable alcohol | |
| h . <i>t</i> -butyl chloride from the suitable alcohol | |

6. Why is the industrial method of preparation of monohalogenated alkanes not generally suitable for laboratory syntheses?

7. In what sense are alcohols bases? Is it correct to call the reaction between an alcohol and hydrochloric acid to form an alkyl chloride and water neutralization? Explain your answer.

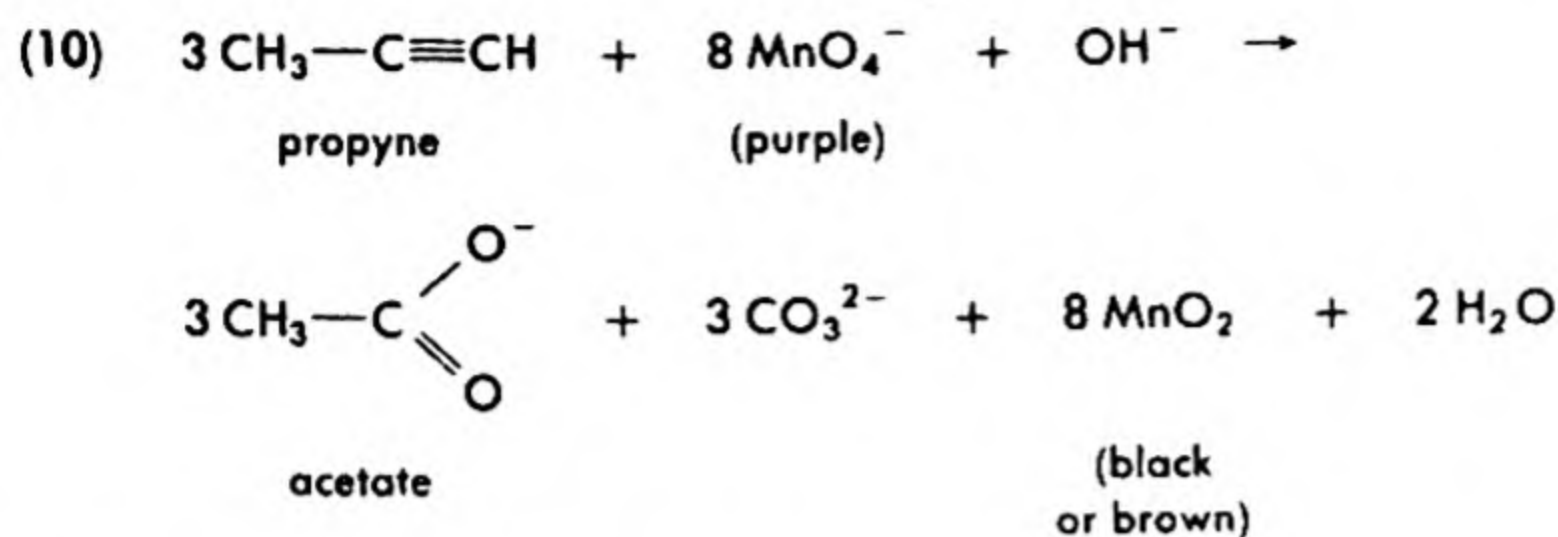
7-2 MULTIPLE BONDS

The π orbitals of multiple bonds are less stable than the σ orbitals of the same bonds. As a consequence, π orbitals are more easily polarized than σ orbitals between the same atoms, and π orbitals involve smaller energy requirements in their reaction pathways than σ orbitals between the same atoms. These factors contribute to much greater reactivity in double or triple bonds than in single bonds between comparable groups. This reactivity, however, extends only to the reactions of the π orbital system, and does not apply in general to reactions of σ orbitals in or attached to the multiple bond. The effect of the π orbital may, indeed, be to decrease activity in some cases, such as displacements in vinyl halides.



A. Olefinic and Acetylenic Bonds

In striking contrast to the unreactivity of carbon-carbon single bonds, carbon-carbon double bonds react rapidly to take up chlorine or bromine, strong acids, and ozone, and readily add hydrogen in the presence of suitable catalysts. Such *addition* reactions are useful in characterizing olefinic bonds, especially the virtually instantaneous decolorization of bromine (without formation of fumes).



B. Carbon-Heteroatom Multiple Bonds

The electronegativity differences in carbon-oxygen and carbon-nitrogen multiple bonds provide positive character on the carbon atom (which is, therefore, electrophilic) and negative character on the heteroatom (which is, therefore, nucleophilic or basic). The greater the electronegativity difference, the more reactive the multiple bond; thus, X—C—Y is more re-

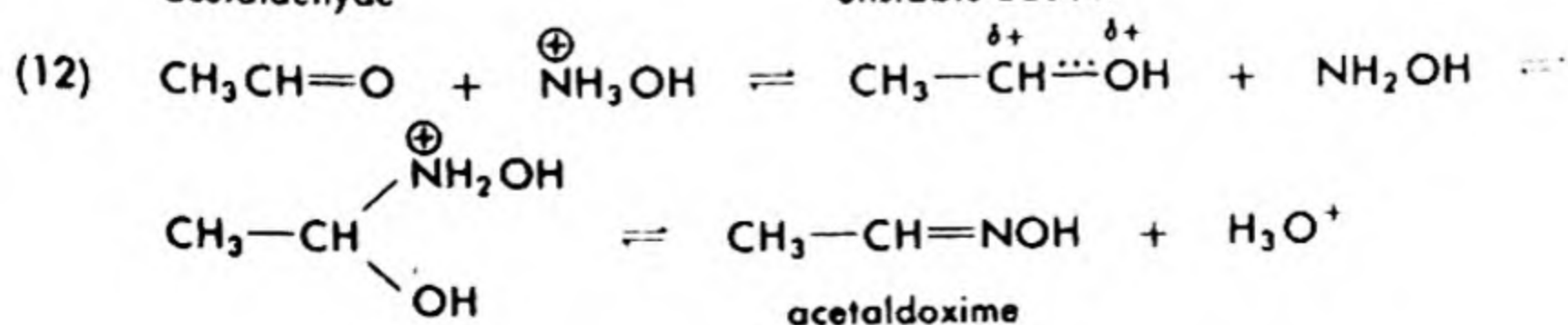
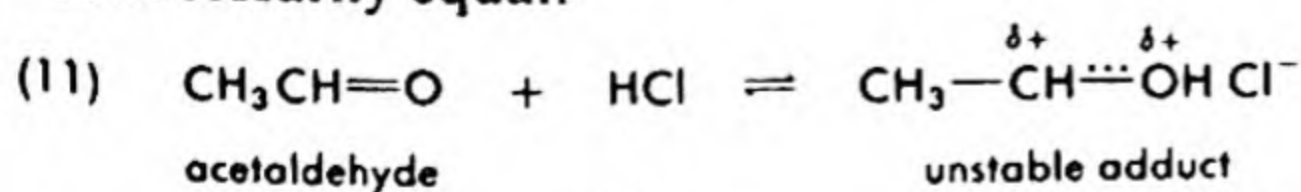
active than X—C—Y , provided that Z does not enhance the electronegativity of N greatly. Also, the reactivity of X—C—Y toward nucleophiles

is in the order $\text{Y} = \text{Cl} > \text{OCR} > \text{OR} > \text{NR—CR} > \text{NR}_2$ in which R =

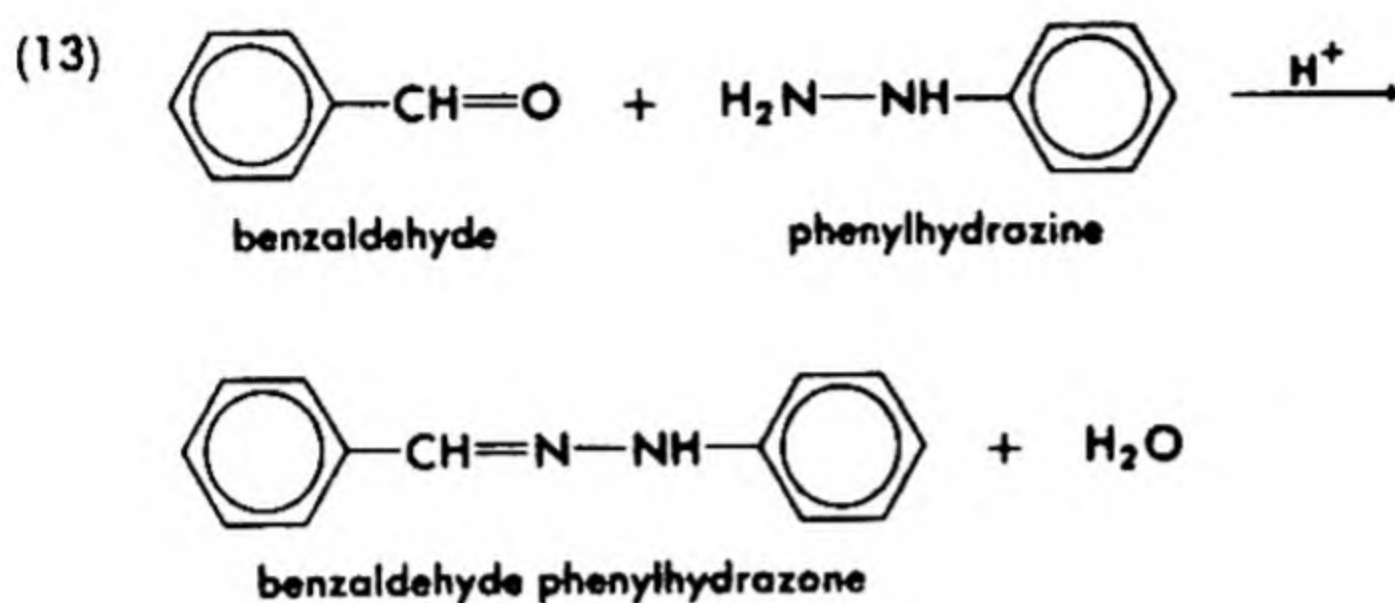
hydrogen or a hydrocarbon group.

In addition to rate considerations, it is necessary to consider stability factors, as many reactions at carbon-heteroatom multiple bonds proceed to a measurable equilibrium. The prediction of equilibrium position from purely electronic considerations is frequently very difficult.

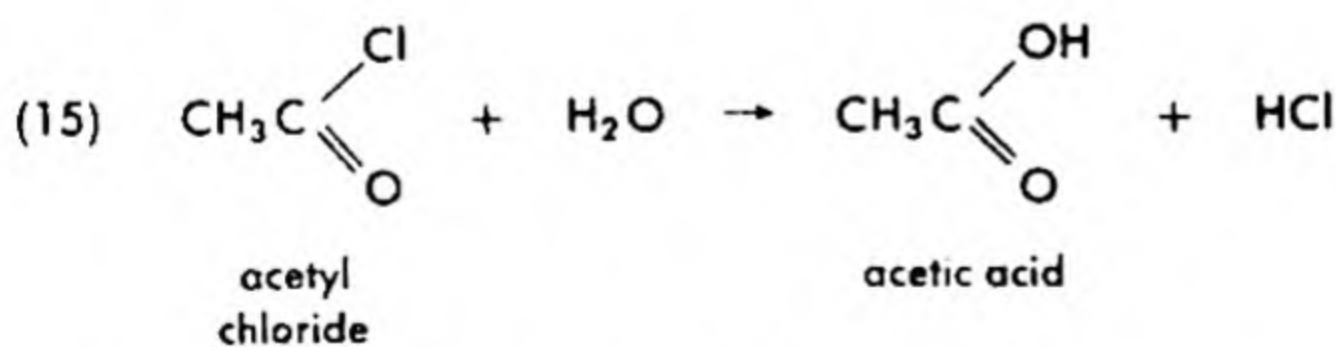
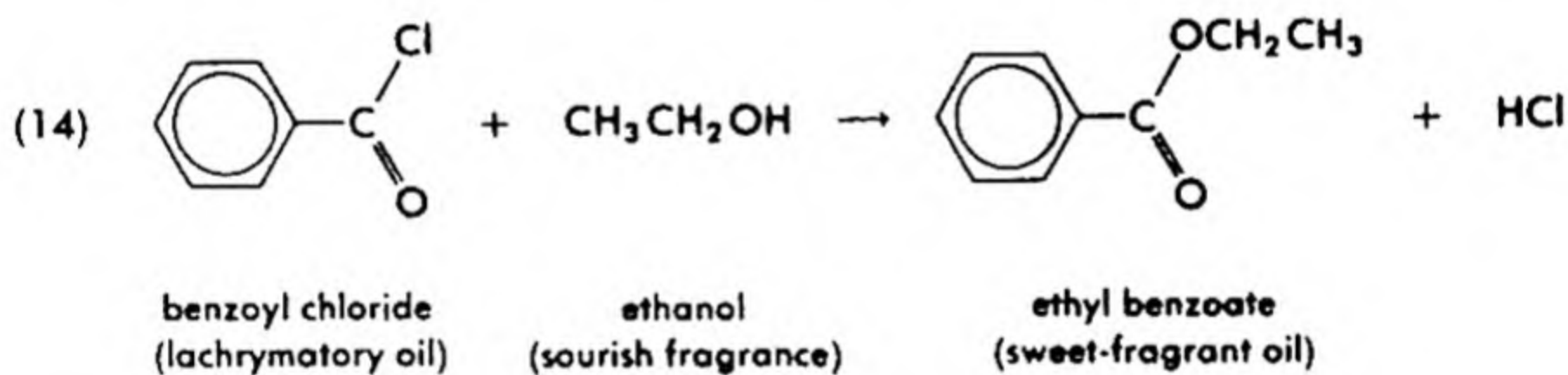
Reactions at the nucleophilic heteroatom are generally of little value in themselves. However, the products, in which the electronegativity of the heteroatom has been greatly increased, generally with the presence of a positive charge, are much more electrophilic than the free reagents. These reactions, therefore, serve to catalyze nucleophilic attack at the carbon atom. The symbols $\delta+$ in eq. (11) represent partial positive charges, not necessarily equal.



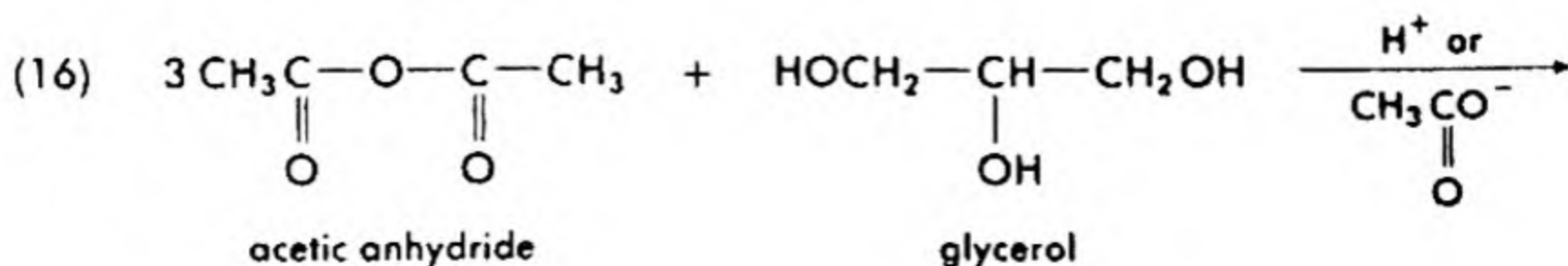
Eq. (12) illustrates the role of acid catalysis in displacement of aldehydic (or ketonic) oxygen. The following displacement, which forms a crystalline derivative of a type useful in characterizing aldehydes and ketones, undergoes similar catalysis.

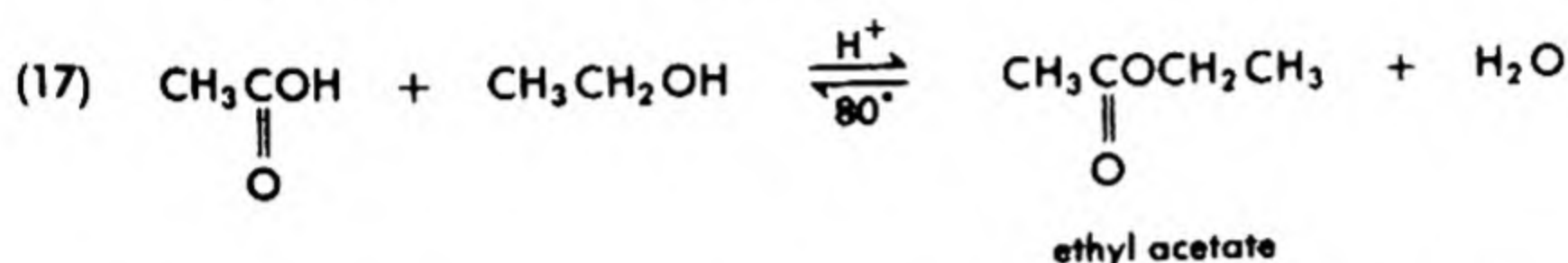
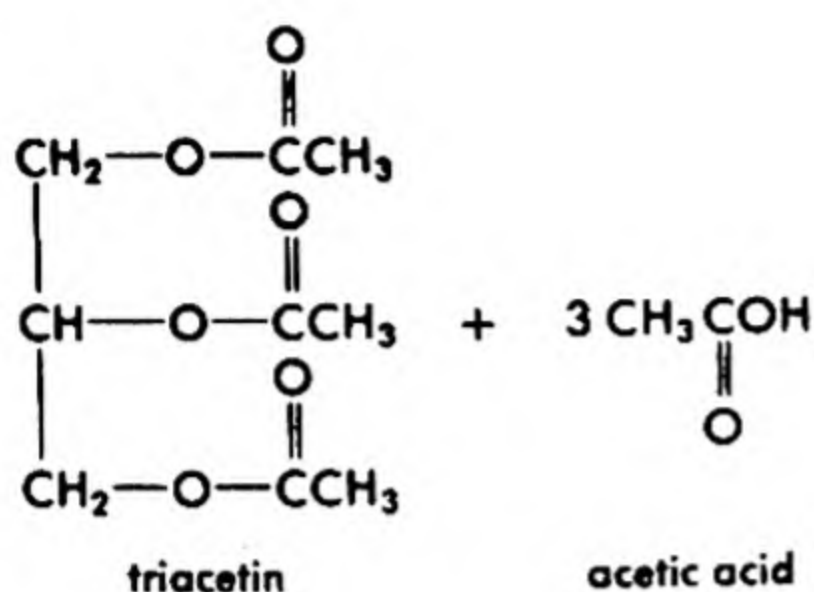


Reactions of acid derivatives, RCOY , in which $\text{Y} = \text{Cl}, \text{OH}, \text{OR}, \text{OCOR}, \text{NH}_2, \text{NHR}, \text{or } \text{NR}_2$, somewhat resemble those of aldehydes and ketones. In the absence of competing equilibria, such as salt formation, the reactivity of these compounds is greater the higher the electronegativity of Y . Equilibria tend toward the less reactive (more stable) species. The following equations illustrate some of the typical conversions.

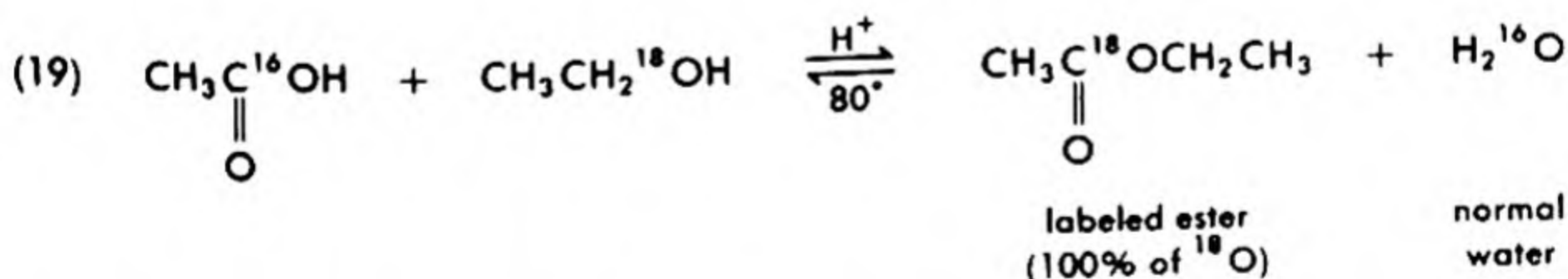
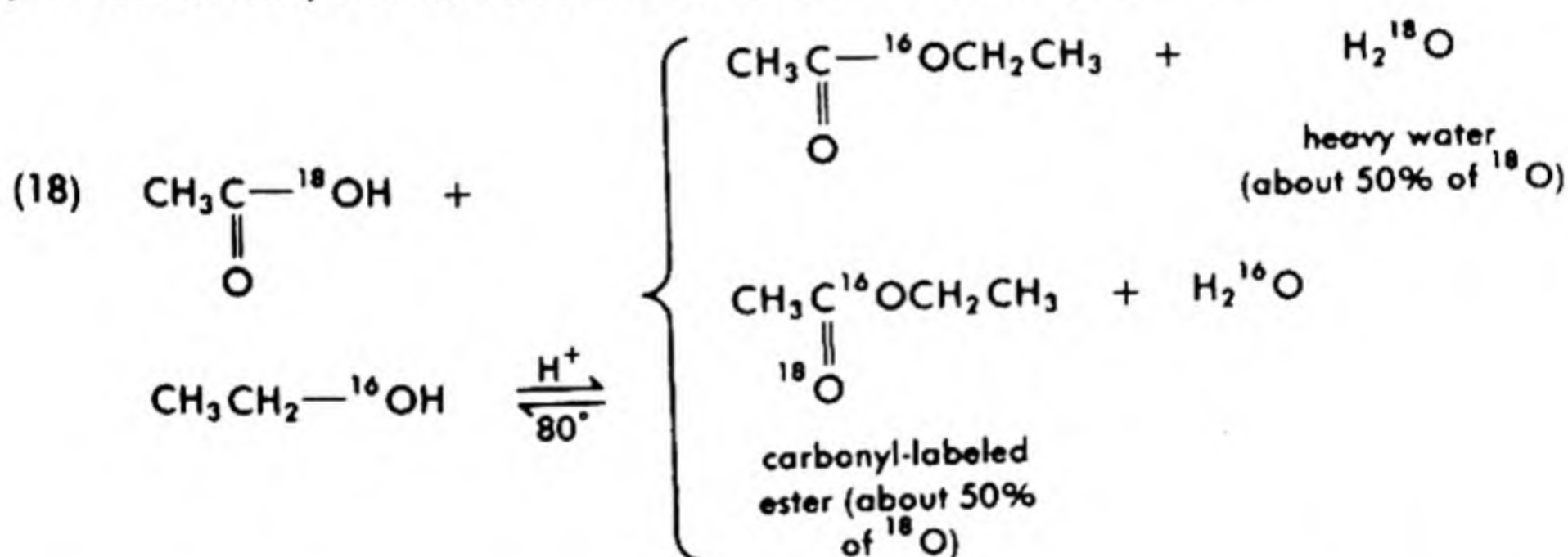


The irreversibility of eq. (15) implies that an acyl halide *cannot* be prepared from an acid and hydrochloric acid. Instead, an inorganic acid halide is used, eq. (23) in §5-2B.

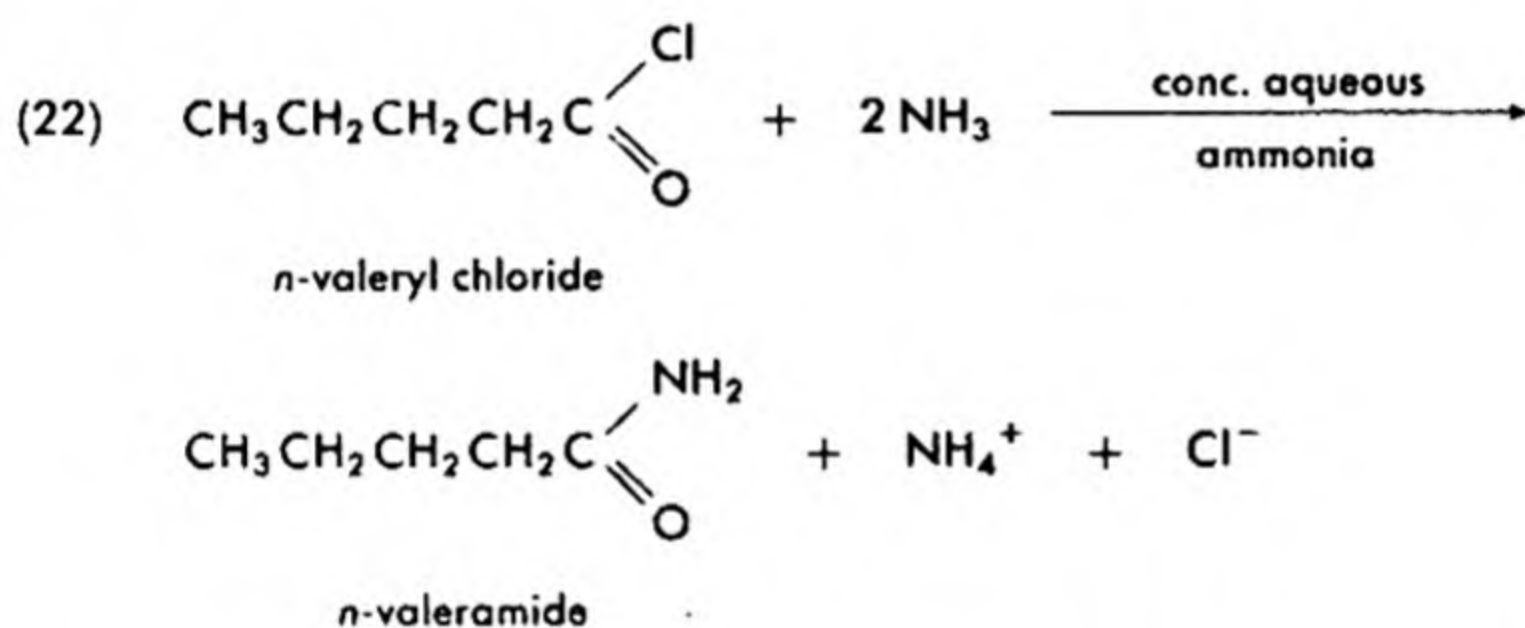
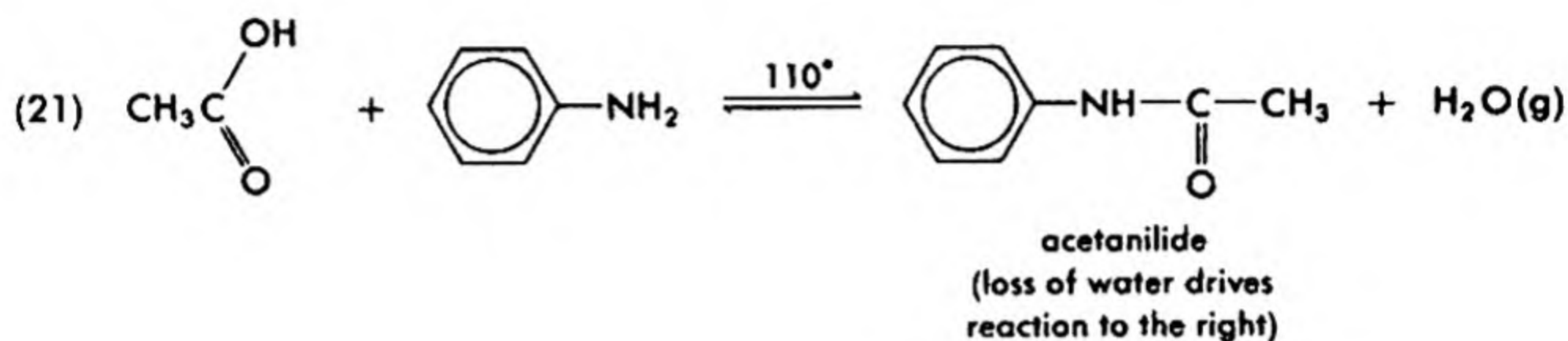
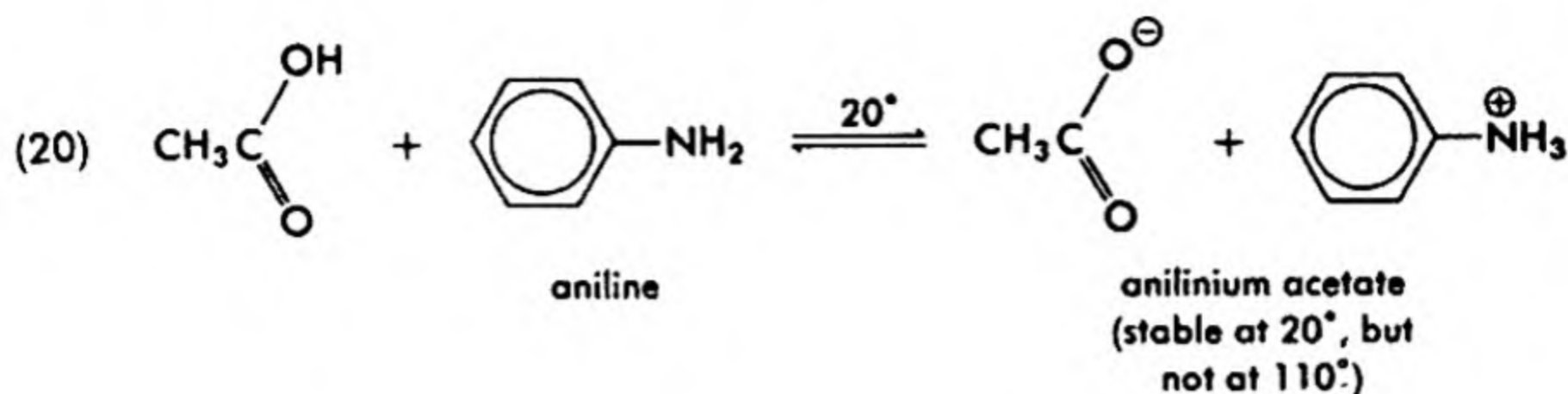




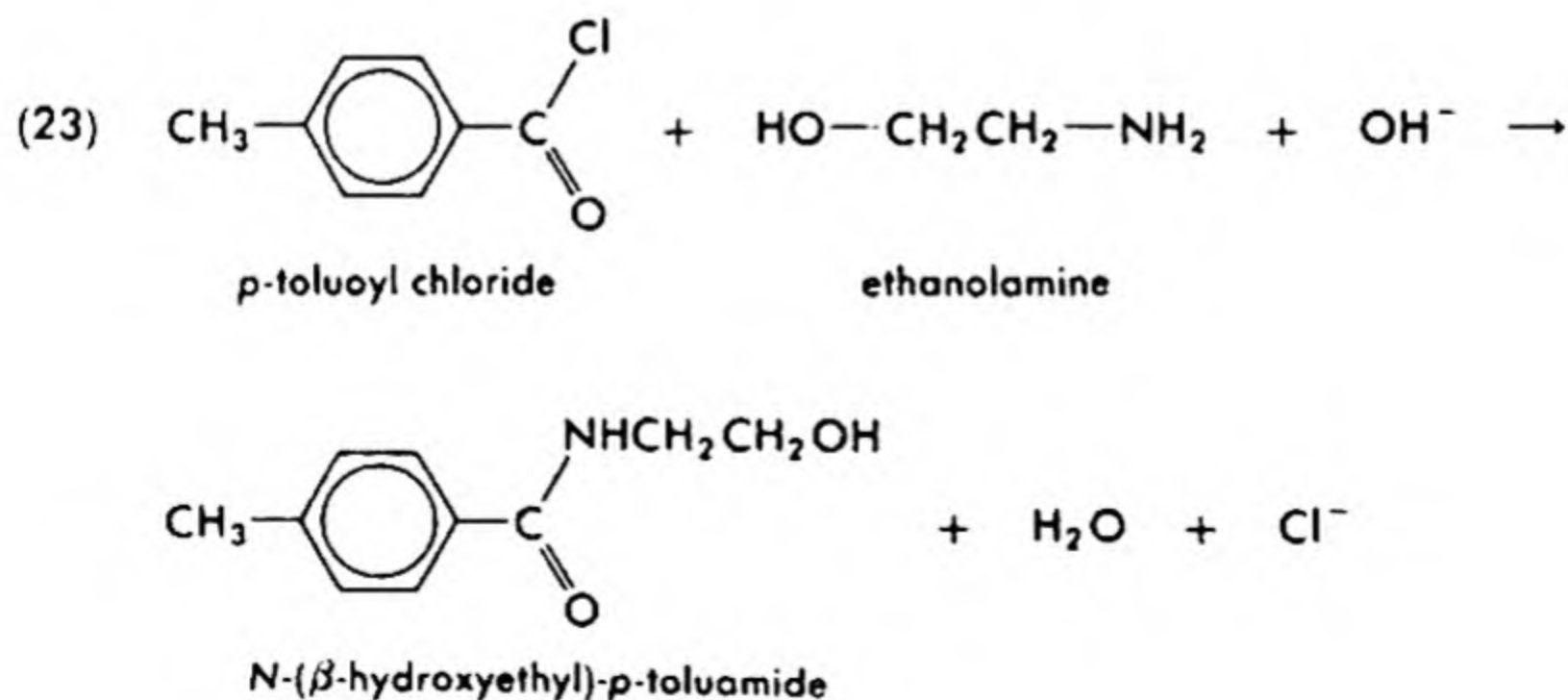
The esterification reaction, eq. (17), is truly reversible. The point of equilibrium depends on the structures of the acid, alcohol, and ester, but is seldom complete either to the right or to the left. Isotope labeling studies show that the alcohol provides only a hydrogen atom in the product water; it is the *acid* that releases a hydroxy group.

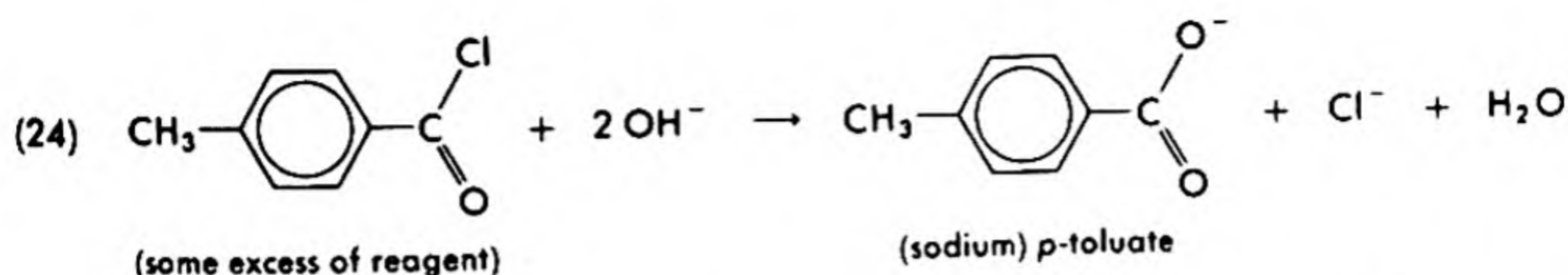


This information implies that the alkyloxy group of the alcohol displaces the hydroxy group of the acid. That the situation is somewhat more complex than this is indicated by the fact that the ^{18}O labeling is actually scrambled between the ester and water in eq. (18), but *not* in eq. (19). An explanation of this and related phenomena is detailed in §17-2 and §17-3A. The student may wish to propose an intermediate for the reaction which would account for the division of labeled oxygen between the water and the carbonyl oxygen of the ester, and check his reasoning by reference to §17-3A.

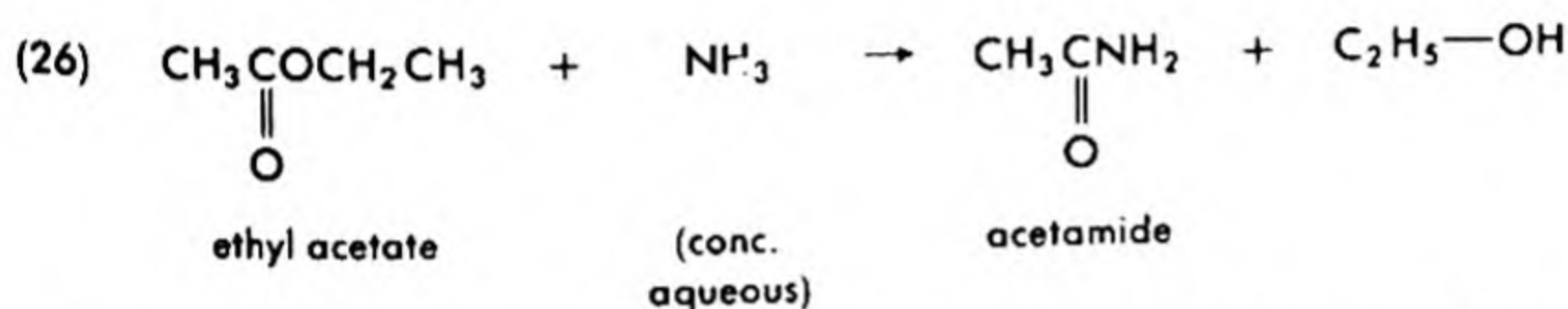
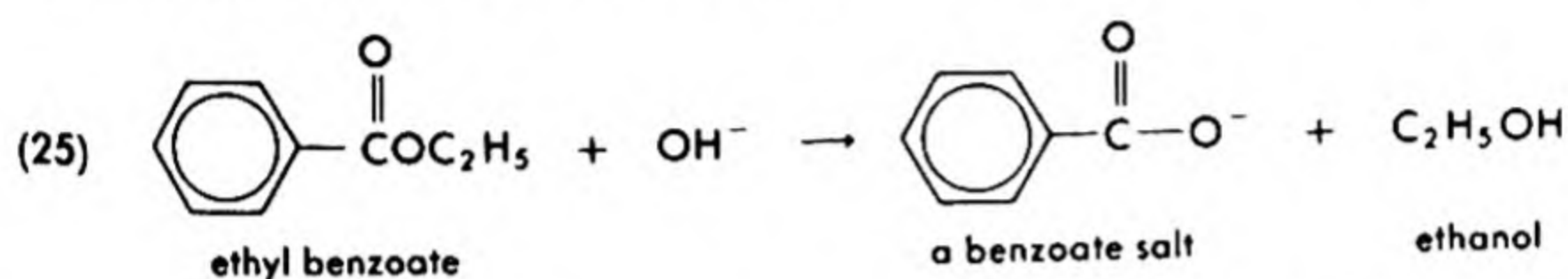


It may be noted that the product hydrogen chloride from the reaction of an acyl chloride and ammonia or an amine neutralizes some of the base as fast as it forms. Thus, to obtain one equivalent of amide, two equivalents of ammonia or amine are required. Since amines are expensive, sodium hydroxide is often used to neutralize the product acid instead of the extra equivalent of amine (Schotten-Baumann procedure). The strong base destroys some of the acyl chloride, which is provided in excess.

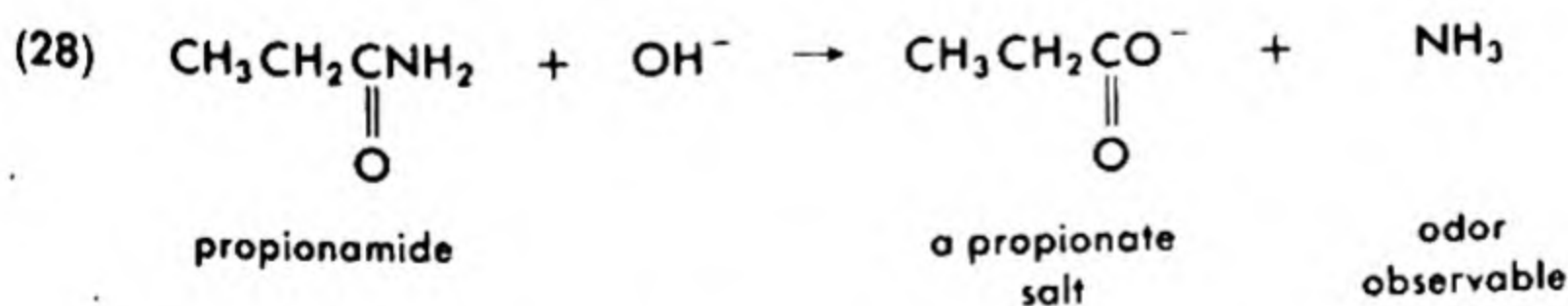
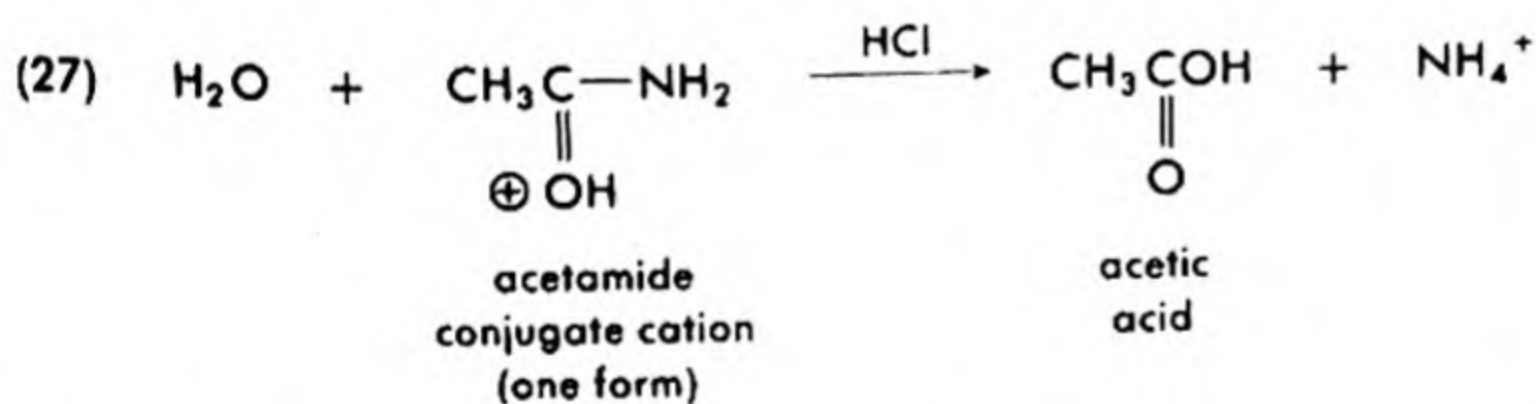




One reaction which has large-scale commercial importance is the reaction of an ester with hydroxide ion. Since fats, which are glyceryl esters, form soaps by this reaction, the process is called saponification.



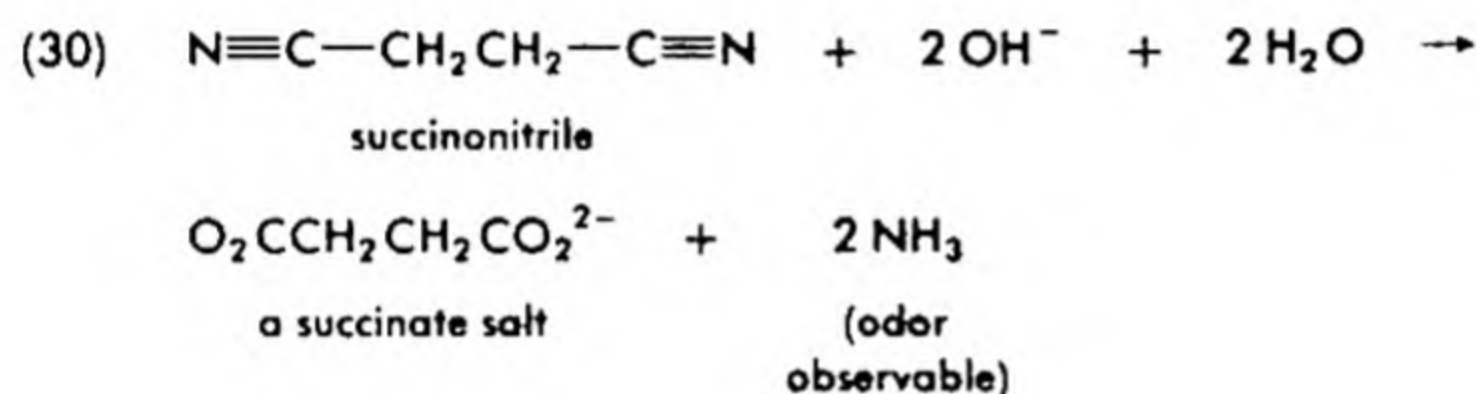
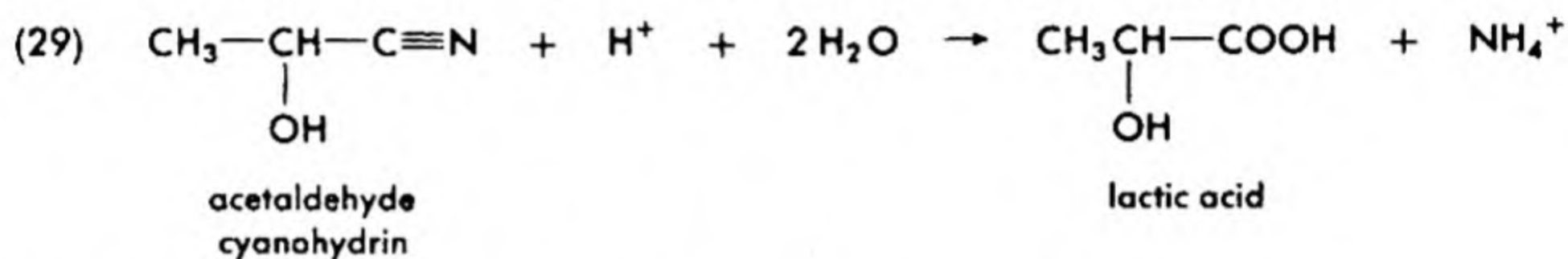
Reaction of an ester with ammonia (or an amine) (eq. 26) goes to completion under the conditions noted. In general, amides react only with very strong nucleophiles, such as hydroxide ion, or as their conjugate acids under conditions such that the acid catalyst also acts as reagent to remove some base from the equilibrium.



In summary, the nucleophiles which react with aldehydes, ketones, functional derivatives of acids and sometimes, under suitable conditions, with carboxylic acids, are hydroxide ion, alkoxide ion, ammonia, ammonia derivatives such as amines, hydrazine, substituted hydrazines and hydroxylamine, water, alcohols, phenols, and other nucleophilic molecules and anions. The more reactive the carbonyl compound, the weaker are the nucleophiles with which it is capable of reacting. These factors are

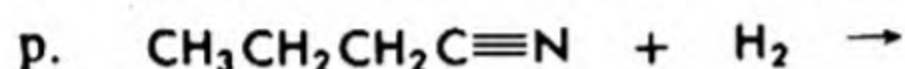
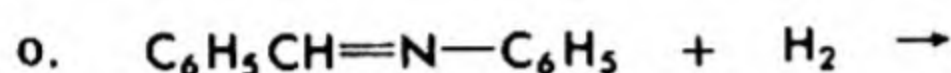
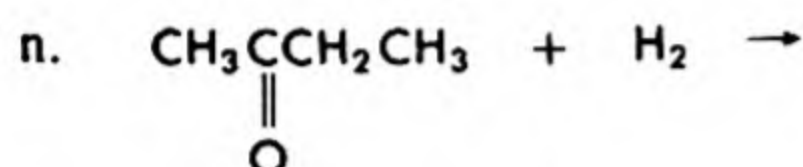
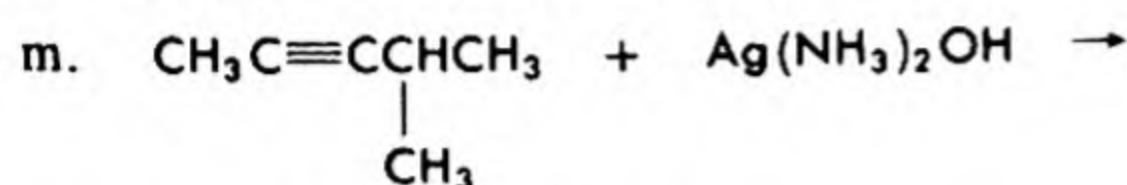
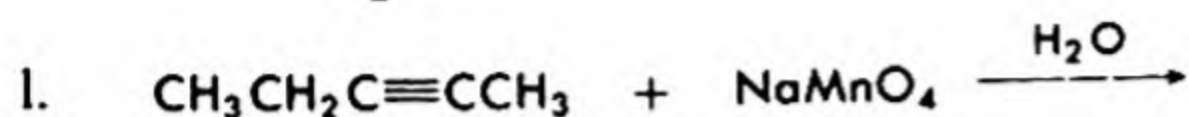
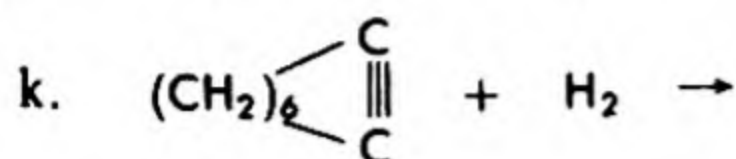
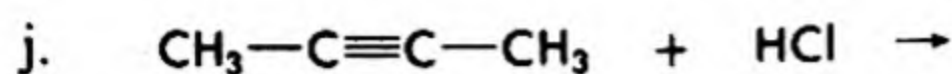
discussed in more detail in reference to reaction pathways in Chapters 17 and 18.

The carbon-nitrogen triple bond, as in nitriles, $R-C\equiv N$, is less reactive than the carbon-nitrogen double bond, as in imines, $R-CH=NH$. This parallels the similar difference in reactivity between alkynes and the olefins formed by the hydrogenation of the alkynes. Of the compounds previously discussed, amides are comparable in reactivity to nitriles. This means that amides are, in general, difficult to prepare by hydration of nitriles, since the amides tend to hydrolyze at rates comparable to their formation. In eqs. (29) and (30), the intermediate amides are not isolated.



QUESTIONS AND PROBLEMS

1. Write an equation to illustrate each of the following.
- a. addition reaction c. saponification
b. esterification d. substitution
2. Write equations for those of the following implied reactions which occur, with conditions. If the compounds do not react under mild conditions, write NR.
- a. $\text{CH}_3\text{—CH=CH}_2 + \text{Cl}_2 \rightarrow$
- b. $\text{CH}_2=\text{CH}_2 + \text{NaOH} \rightarrow$
- c. $\text{CH}_3\text{—CH=CH—CH}_3 + \text{H}_2\text{SO}_4 \xrightarrow{\text{(conc.)}}$
- d. $(\text{CH}_3)_2\text{C=C(CH}_3)_2 + \text{H}_2\text{O} \rightarrow$
- e. $\text{CH}_3\text{—CH=CH}_2 + \text{H}_2 \rightarrow$
- f. $\text{CH}_3\text{CH}_2\text{CH=CH}_2 + \text{NaMnO}_4 \xrightarrow{\text{H}_2\text{O}}$
- g. $\text{CH}_3\text{—C}\equiv\text{CH} + \text{Br}_2 \rightarrow$
- h. $\text{HC}\equiv\text{CH} + \text{NaOH} \rightarrow$
- i. $\text{CH}_3\text{CH}_2\underset{\begin{array}{c} | \\ \text{CH}_3 \end{array}}{\text{CH}}\text{C}\equiv\text{CH} + \text{Ag(NH}_3)_2\text{OH} \rightarrow$



3. What familiar named test is used to distinguish between saturated and unsaturated hydrocarbons? What is observed when the test is used? Describe the results for both a saturated and an unsaturated hydrocarbon.

4. To test for unsaturation, a compound can be treated with bromine in what solvent? This solvent is used to facilitate observation of what substance? How significant is this observation?

5. Compare alkanes, alkenes, and alkynes with respect to characteristic type of reaction and relative ease of reaction.

6. Show how hexane and 2-hexene can be distinguished chemically in three ways. Describe the observations in each test.

7. Show how the following compounds can be distinguished by simple chemical tests. Describe the observed differences in results of each test. Write equations for any reactions that occur.

- pentane, 1-pentene, and 1-pentyne
- cyclopentane, ethylcyclopropane, and 1-pentene
- 1-heptyne and 2-heptyne
- propylcyclopropane and 2,3-dimethyl-2-butene
- methanol and *n*-hexane
- 1-hexyne and ethanol
- ethyl *n*-butyl ketone and *n*-butyl ether
- n*-butyraldehyde and ethanol
- acetic anhydride and *n*-valeryl chloride
- ethyl acetate and 2-butanone

- ethyl *n*-butyrate and *n*-butyl ether
- acetyl chloride and isopropyl chloride
- ethanol and *n*-butylamine
- triethylamine and *n*-propyl ether
- n*-butyronitrile and *n*-butylamine
- benzamide and 3,4-xylamine
- propionanilide and aniline hydrochloride
- n*-butyramide and tri-*n*-butylamine

8. How do cyclopropane and cyclobutane differ from cyclopentane and cyclohexane? How do cyclopropane and cyclobutane differ from ethylene? Base your answer on chemical properties.

9. Write equations for any reactions that occur in the following mixtures of substances under moderate conditions. Use structural formulas. Indicate essential special conditions. If no reaction occurs, write the formulas of the reagents and NR.

- | | |
|---|---|
| a. butanal + hydroxylamine | r. isopropyl trimethylacetate + dilute sodium hydroxide solution |
| b. 1-butanol + hydroxylamine | s. propyl methanoate + concentrated ammonium hydroxide |
| c. diethyl ketone + hydroxylamine | t. malonyl chloride + dilute sodium hydroxide solution |
| d. cyclopentanone + phenylhydrazine | u. 2-methylpropanoyl chloride + concentrated ammonia solution |
| e. <i>n</i> -valeraldehyde + semicarbazide ($\text{H}_2\text{NNHCONH}_2$) | v. phthalic anhydride + dilute sodium hydroxide |
| f. 2-methylcyclohexanone + hydrogen | w. succinic anhydride + concentrated ammonium hydroxide |
| g. 1-propanol + ethanoic acid | x. methylamine + water |
| h. butanoic acid + hydrochloric acid | y. methylethylamine + acetic anhydride + dilute sodium hydroxide |
| i. benzoic acid + thionyl chloride | z. dimethylisobutylamine + acetic anhydride + dilute sodium hydroxide |
| j. benzoic acid + <i>n</i> -propyl alcohol | aa. <i>n</i> -butyramide + dilute sodium hydroxide |
| k. ethyl <i>n</i> -butyrate + isopropyl alcohol | ab. <i>n</i> -valeronitrile + dilute sodium hydroxide |
| l. methyl isobutyrate + water | ac. formamide + dilute hydrochloric acid |
| m. <i>n</i> -valeryl chloride + water | ad. <i>n</i> -pelargonitrile + hydrogen + platinum |
| n. isovaleryl chloride + isobutyl alcohol | |
| o. caproic anhydride + <i>sec</i> -butyl alcohol | |
| p. crotonic anhydride + water | |
| q. methacrylic acid + concentrated ammonia solution | |

10. Each compound to be prepared below can be made in one step from the suggested starting material. Write equations for the required reactions, including necessary special conditions. Use structural formulas.

- | | |
|---|---|
| a. ethyl bromide from an alkene | f. ethyl hydrogen sulfate from ethylene |
| b. 1,2-dibromobutane from the suitable hydrocarbon | g. 1-bromocyclooctene from the suitable hydrocarbon |
| c. 1,1-dichloroethane from the suitable hydrocarbon | h. 1,3-dibromobutane from the suitable hydrocarbon |
| d. ethylene from acetylene | i. 1,4-dibromobutane from the suitable hydrocarbon |
| e. 2,2,3,3-tetrabromobutane from the suitable hydrocarbon | |

- | | |
|--|--|
| j. acetaldehyde from acetylene | u. <i>n</i> -butyramide from methyl <i>n</i> -butyrate |
| k. ethylbenzene from suitable halides | v. formic acid from ethyl formate |
| l. 1,2-dichloropropane from an unsaturated hydrocarbon | w. propionamide from propionyl chloride |
| m. 1,1-diiodoethane from an unsaturated hydrocarbon | x. ethyl isobutyrate from an anhydride and an alcohol |
| n. acetaldoxime from acetaldehyde | y. benzoyl chloride from benzoic acid |
| o. acetone phenylhydrazone from the carbonyl compound and suitable reagent | z. <i>N</i> -methylacetamide from the suitable anhydride and amine |
| p. isopropyl alcohol from a suitable carbonyl compound | aa. acetanilide from the suitable amine and acid |
| q. benzyl alcohol from a suitable carbonyl compound | ab. acetamide from an ester |
| r. <i>n</i> -butyryl chloride from the suitable acid | ac. isobutyramide from isobutyric acid |
| s. methyl <i>n</i> -butyrate from an alcohol and an acid | ad. sodium propionate from propionitrile |
| t. <i>n</i> -butyl acetate from an alcohol and an acid | ae. propionic acid from propionitrile |
| | af. ethylamine from acetonitrile |

11. Arrange the following compounds in the order of increasing reactivity toward hydrolysis.

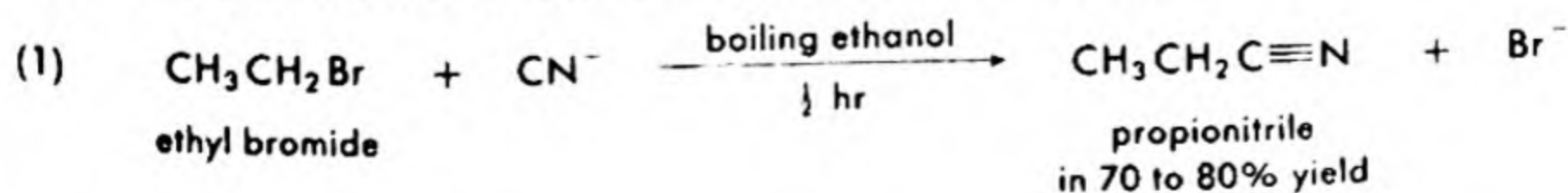
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| a. acetic anhydride, acetyl chloride, ethyl acetate | b. <i>n</i> -hexyl chloride, hexanoyl chloride, benzoyl chloride |
|---|--|

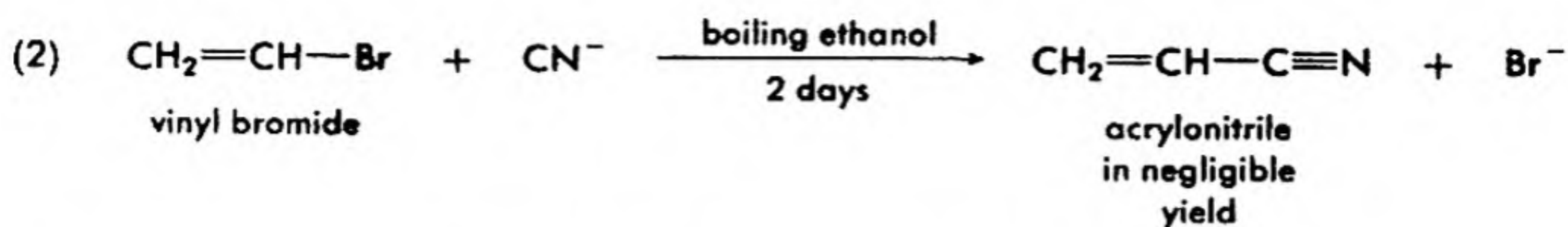
12. What effects would you expect a trace of added concentrated sulfuric acid to have on eq. (21), §7-2B? What effect would equivalent or excess concentrated sulfuric acid have on this equilibrium? Explain your answers.

13. In eq. (23), §7-2B, why is the amino group attacked in preference to the hydroxy group? What would be the effect on this reaction of too large an excess of the *p*-toluoyl chloride?

7-3 GROUP INTERACTIONS

The simple relationships which hold for reactions of saturated monofunctional compounds are often drastically modified when more than one function is present. This is especially so for compounds that contain a functional group on an unsaturated carbon atom. A simple example is vinyl bromide, which does not react at all readily like saturated alkyl bromides. In the reaction of vinyl bromide with cyanide the reaction is so





slow that side reactions, that is, competing and consecutive reactions, destroy most of the acrylonitrile as fast as it forms. (See also eq. (1), §7-2.)

A. Conjugation and Resonance

Structurally, a system of alternating multiple and single bonds is said to be conjugated (§5-1C). What this means in terms of chemical properties provides a fascinating chapter in the history of organic chemistry that began about 1870 and may not be completed for another century. New and unforeseen aspects of conjugation turn up frequently in the chemical literature. Historically, benzene initiated the study, and, with the help of modern theory, benzene provides a convenient point of entry for the contemporary student.

(1) *Benzene and Aromaticity.* We have seen (§4-1G(3)) that the structure and properties of ethylene may be computed by a quantum-mechanical treatment as a twelve-electron system in which ten of the electrons occupy five stable sigma orbitals, while the remaining pair occupies a somewhat higher (but still stable) π orbital. If one considers just the carbon-carbon double bond (Figs. 4-15B and 4-17), two electrons occupy the σ orbital and two the π orbital. One should note again that the π orbital is more stable than its parent p atomic orbitals by the amount of delocalization energy of the system. One may now treat benzene as an analogous thirty-electron problem. Of the thirty electrons, twenty-four are utilized to form the six carbon-hydrogen bonds (sigma molecular orbitals) and the six sigma bonds of the carbon-carbon system (see Fig. 7-2A). Presumably these sigma orbitals are similar to that shown in Fig. 4-15B and those discussed in §4-1F. Each carbon atom thus uses its s atomic orbital and two of its three p orbitals to make the hybridized sp^2 atomic orbitals utilized in these sigma molecular orbitals. This gives the correct geometry, as sp^2 orbitals are planar and have 120° angles between lobes, precisely the angle of a regular hexagon.

The more interesting part of the benzene problem concerns the remaining six electrons. Remaining on each of the six carbon atoms is one p orbital and one electron. We may now consider the results of some possible quantum mechanical treatments of these six p atomic orbitals. As a first assumption we might consider forming molecular orbitals from pairs of adjacent atomic orbitals, that is, treating benzene as if it had three isolated double bonds. This would give the energy diagram shown in Fig.

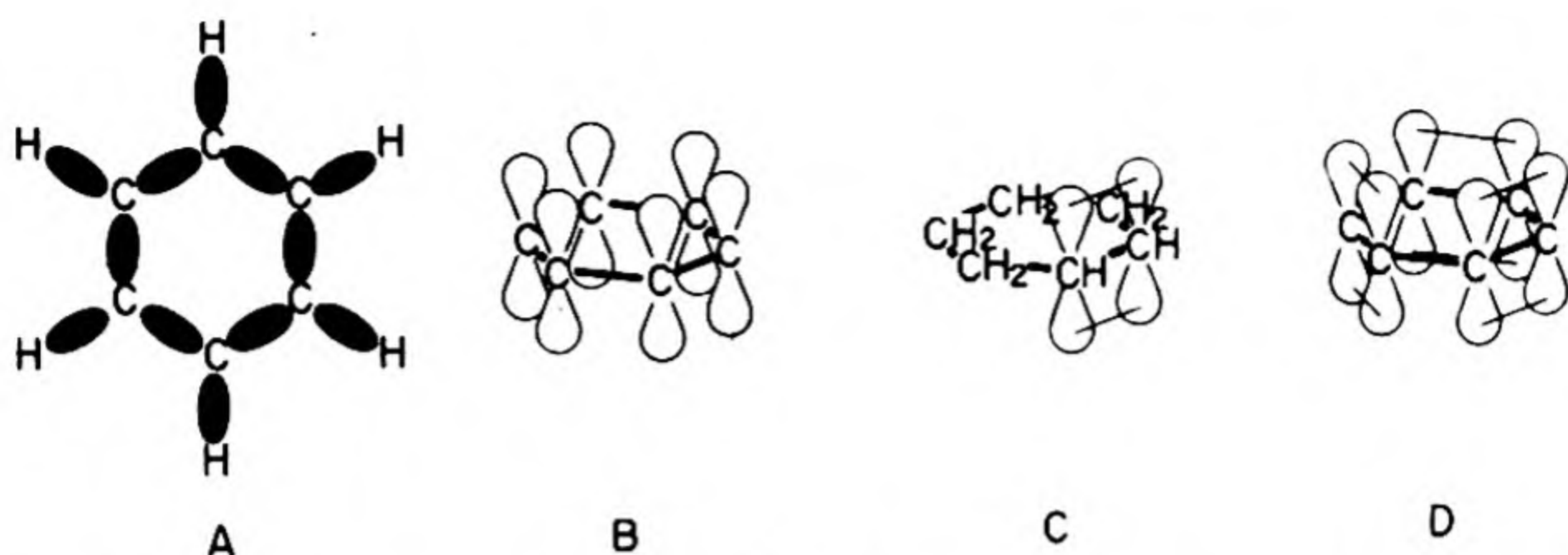


Fig. 7-2. Orbital Systems Concerned with Benzene Structure. (A) The twelve σ MO's of the benzene ring system, (B) six atomic p orbitals available for delocalization in benzene, (C) π Orbital in cyclohexene, (D) π overlap assumed in a given Kekulé structure having energy equivalent to diagram Fig. 5-16A.

7-3A, where there are shown three identical π bonding orbitals (as well as the three π^* antibonding orbitals), each with delocalization energy equivalent to the π orbital in cyclohexene (Fig. 7-2C and D). These three bonding MO's would hold the six remaining p electrons. This computation would give us a model for benzene which is equivalent to one of the Kekulé structures (Fig. 7-4C or H).

This model has been tested as follows: Hydrogenation of cyclohexene consumes one mole of hydrogen with the evolution of 28.6 kcal./mole of heat. If benzene were the hypothetical Kekulé cyclohexatriene (Figs. 7-2D

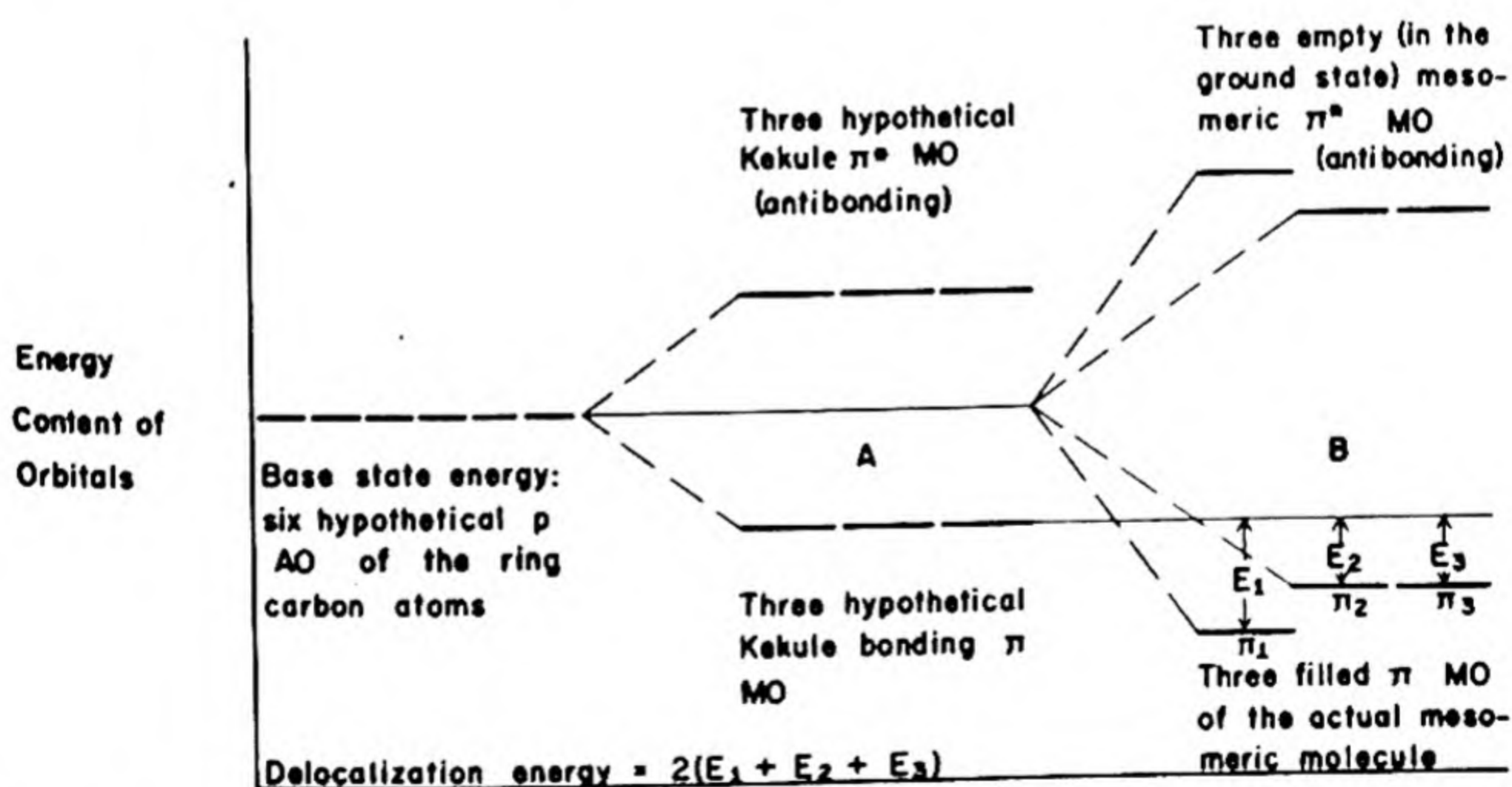


Fig. 7-3. Energy Diagram for Molecular Orbital Formation from p Orbitals in Benzene. (A) Treatment as if benzene were 1,3,5-cyclohexatriene (one of the Kekulé structures), (B) treatment of all six p orbitals together.

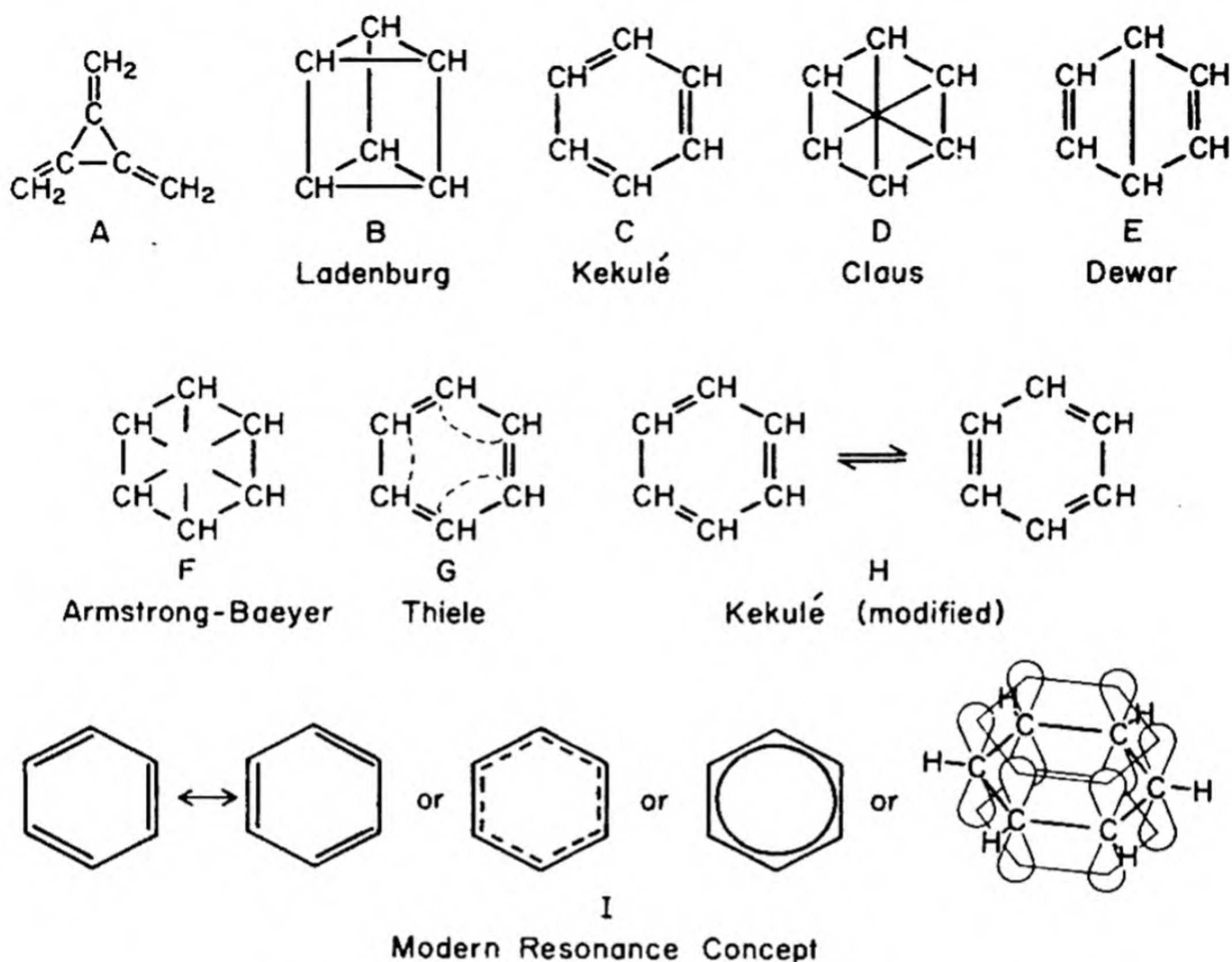


Fig. 7-4. Proposed Structures of Benzene.

and 7-3A), the heat of hydrogenation of each double bond would be approximately the same as that of the double bond of cyclohexene, and the total heat of hydrogenation would be about 3×28.6 or 85.8 kcal./mole. In fact, however, the heat of hydrogenation of benzene is only 49.8 kcal./mole, so that benzene is 36.0 kcal./mole more stable than the Kekulé model of noninteracting double bonds would lead us to predict. An analogous calculation using heat of combustion data gives a similar result. Benzene is more stable (i.e., contains *less* energy) than calculated by a large discrepancy which is well outside experimental error.

An alternative MO calculation result is shown in Fig. 7-3B. Here all six p atomic orbitals are treated together to give complete overlap, with each MO encompassing all six atoms (rather than each MO being restricted to a pair of atoms). Now we again get three bonding MO's and three anti-bonding MO's, but as a comparison of A and B shows, the three new bonding orbitals are considerably more stable than those calculated in A.

Heretofore we have used the terms "resonance energy" or "delocalization energy" in reference to the energy difference between the atomic and

the molecular orbitals. However, these terms have been used by organic chemists in a somewhat different sense and we will use them in this sense in the remainder of the book. We will now define resonance energy or delocalization energy as the difference in energy between that calculated for a model with an electron system capable of representation by a conventional bond structure and that observed for an actual molecule not capable of conventional structural representation. For benzene, the delocalization energy is that calculated for the Kekulé model (determined in principle from Fig. 7-3B by adding the energy contents of the three Kekulé π orbitals) less that of the real molecule (again determined, in principle, but not in practice, by the sum of the energy levels of π_1 , π_2 , and π_3). This leads to the new energy level diagram shown in Fig. 7-5, which indicates the ordinary usage of these terms of energy differences.

The foregoing discussion is intended to provide a semimathematical and physical background to a concept which has found considerable use in organic chemistry. As we have noted, the conventional method of representation of molecules with lines (or pairs of electrons) as bonds does not permit us to describe benzene accurately with only one structural formula. If, however, we imagine that the Kekulé structural formulas are

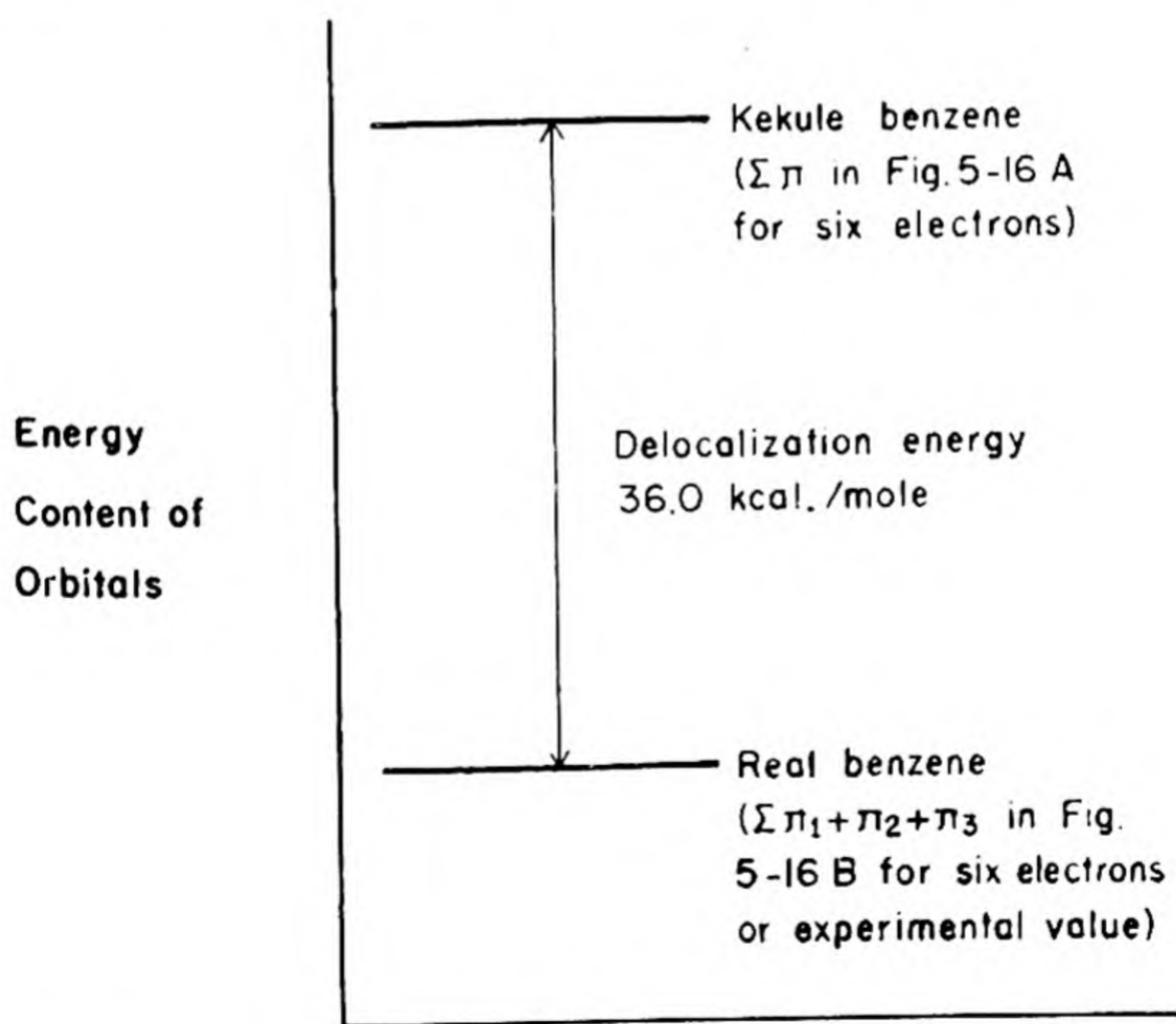


Fig. 7-5. Resonance Energy Diagram for Benzene. Top line is hypothetical.

superimposed, we would have a molecule represented by the formula III, in which each carbon-carbon bond is intermediate between single and double and all are identical.



It is convenient, for a number of reasons which will become apparent during the course of study, to discuss real molecules in terms of conventional structures such as I and II, by using the language of the theory of resonance (mesomerism). In this theory, structural formulas such as I and II are called *valence bond structures* or *canonical structures*, and actual molecules are said to be *resonance hybrids* or *mesomers* (Gk. *mesos*, between, and *meros*, parts) of these structures, represented as IV. The distribution of electrons in a molecule can be approximated quite well by assuming, for example, that benzene is a hybrid of I and II. As electron distribution is pertinent to reactions and reactivity, consideration of valence-bond structures in discussing these is useful. Chemists use a double headed arrow (\longleftrightarrow) to link the valence-bond structures to show that they are *not real species*, but are simply formulas that must be *considered together* to understand the real molecule. This has often been misunderstood or misapplied, with the erroneous assumption made that there is an equilibrium between the valence-bond structures, that is, that some of the molecules have one of the structures and some the other(s), or that part of the time a given molecule has one structure and part of the time it has the other(s). As the molecular orbital discussion above indicates, this interpretation is quite incorrect, but valence-bond structures must be considered simply as a means, *taken together*, of conveniently representing electron distribution in molecules. Chemists may say that the valence-bond structures "contribute" to the actual molecule. The equivalent language, that the molecule "resonates" between the valence-bond structures, could lead to confusion and thus should be avoided.

The general theory of resonance or of mesomerism can be summarized in the following rules (which have some interesting exceptions not considered here):

1. Whenever one may write two or more valence bond structural formulas for a molecule (or other chemical entity) which *differ from each other only in the position of electrons*, then none of the formulas represents the actual molecule, but the actual molecule is a resonance hybrid to which each of the structures contributes.

2. When the several structures differ in energy content, the actual molecule is more like the one of lower energy content (i.e., contributions

from the several structures are not necessarily identical, and greater contributions are made by low-energy structures than by high-energy ones).

3. Electron distribution in an actual molecule can be estimated from a consideration of the hybrid structure or of the contributions of the several valence-bond structures. Other physical properties (except energy content) can also be estimated in this way.

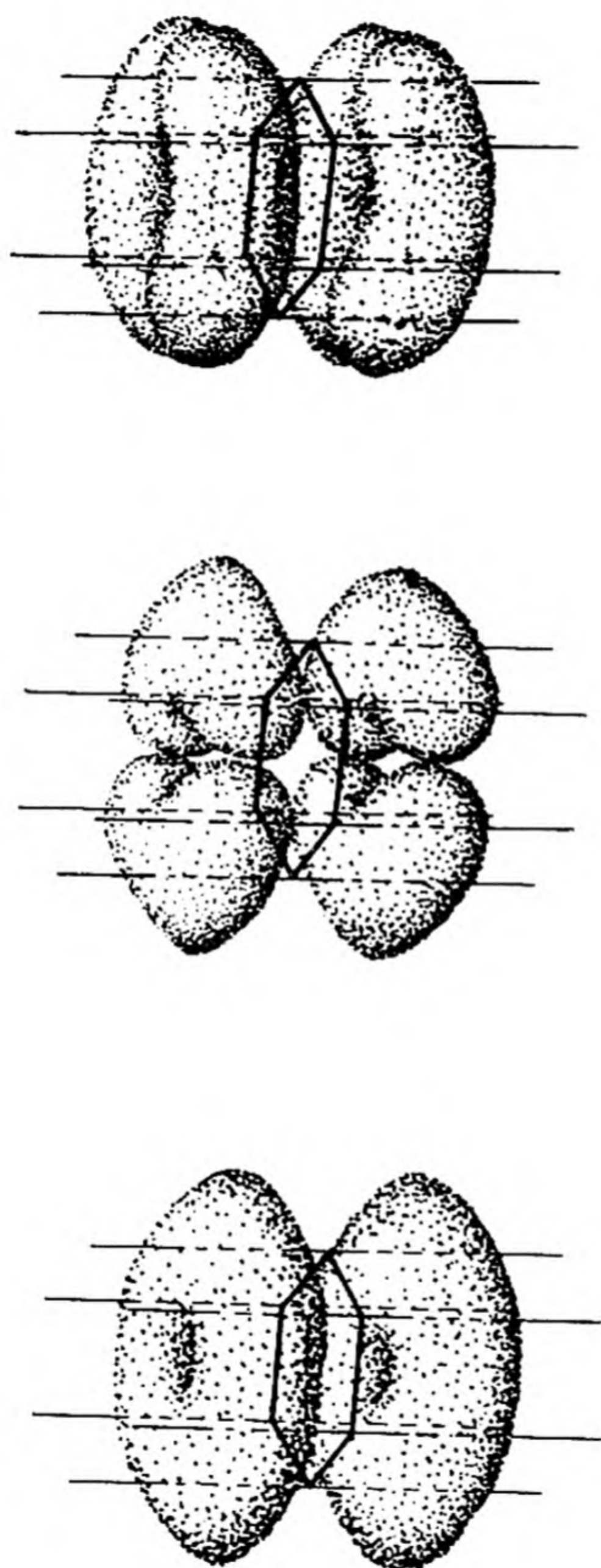
4. The energy of an actual molecule is always less than that estimated for any of the valence-bond structures; the difference between the energy of the lowest-energy canonical structure and that of the actual molecule is termed the *resonance*, *mesomeric*, or *delocalization energy*. The magnitude of this difference depends upon the differences in energy of the hypothetical valence-bond structures; when these differences are small, then electron delocalization is great and resonance energy is great. When one structure is substantially lower in energy content (more stable) than the other(s), the resonance energy is low and as indicated in (2), the higher-energy structures make less contribution to the hybrid molecule.

The delocalized π molecular orbitals of benzene can be represented descriptively. It is simplest to describe the lowest-lying MO (π_1 of Fig. 7-3B). It is shaped much like two irregular doughnuts, one lying above the plane of the ring carbon atoms, and an identical half lying below the plane (Fig. 7-6A). This orbital holds two of the six π electrons. The remaining two bonding orbitals (π_2 and π_3 of Fig. 7-3B), although of equal stability, are of different relative orientation (Fig. 7-6B and C). Each of these orbitals holds two electrons.

The special stability of benzene is not common to all closed conjugated systems. For example, calculations indicate that cyclobutadiene has the same energy content for delocalized "aromatic" orbitals (i.e., benzene-like orbitals) as for nonoverlapping double bonds; cyclooctatetraene is calculated to be about 6 kcal./mole more stable as four double bonds than as an aromatic system, and consequently, has no tendency to assume a strained planar conformation.



Only systems of $4n + 2$ available p -electrons form unusually stable conjugated systems (Hückel's rule). Although there is some quantum mechanical justification for this rule, it may best be stated to be a description of every closed conjugated system studied thus far. Another requisite is that the closed system must be capable of existence essentially strain-free in a single plane (or nearly so). The fused aromatic systems, such as naphthalene ($n = 2$), anthracene ($n = 3$), and phenanthrene ($n =$



A. Aromatic π_1 MO B. Aromatic π_2 MO C. Aromatic π_3 MO

Fig. 7-6. Molecular Orbitals in Delocalized Benzene Model (closely approximating actual benzene).

3) admirably fit this description. They are thus characterized by large resonance energies (Table 7-1).

TABLE 7-1. Resonance Energies of Arenes

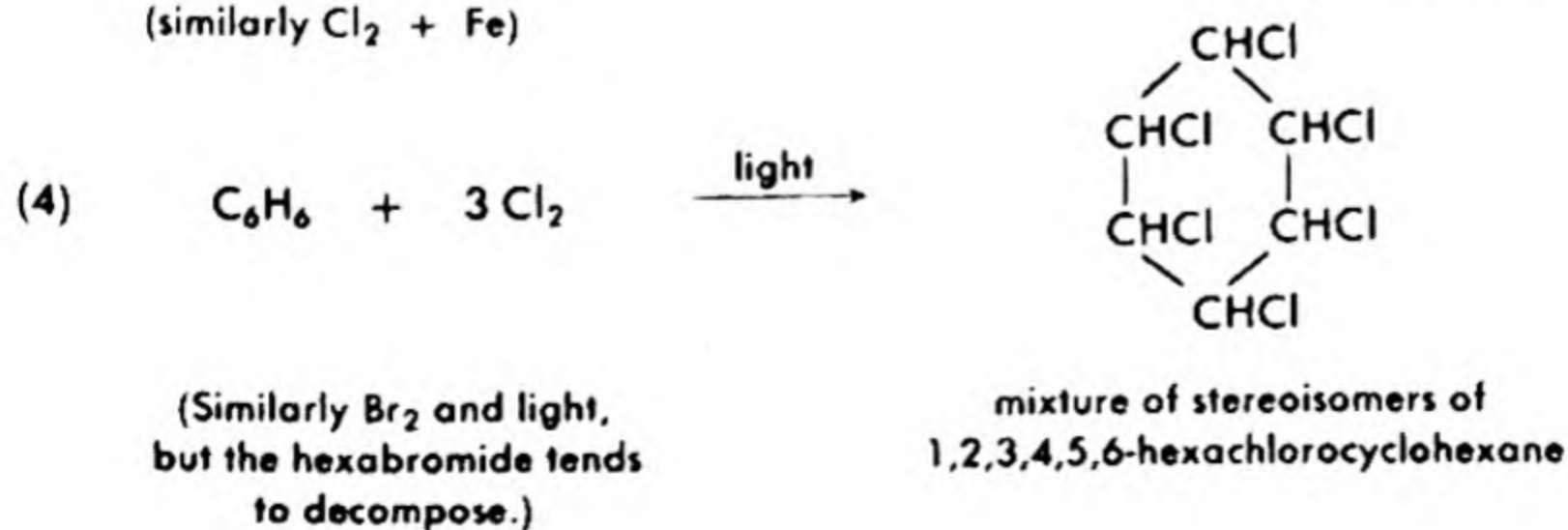
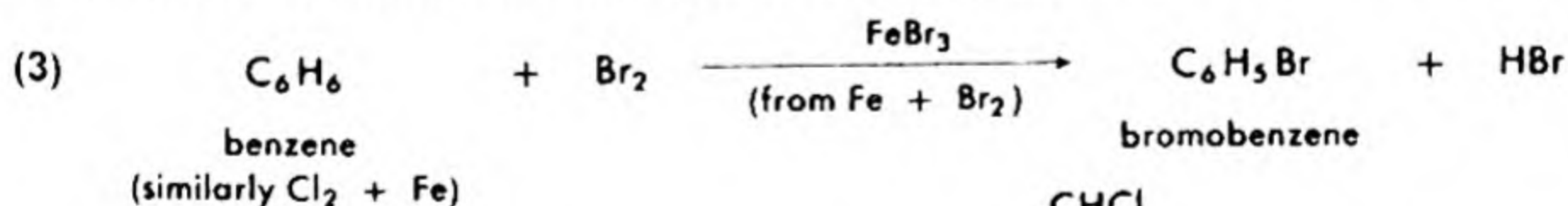
Compound	n (in $4n + 2$)	Resonance energy, kcal./mole ^a
Benzene	1	35-42
Naphthalene	2	61-77
Anthracene	3	84-116
Phenanthrene	3	90-130

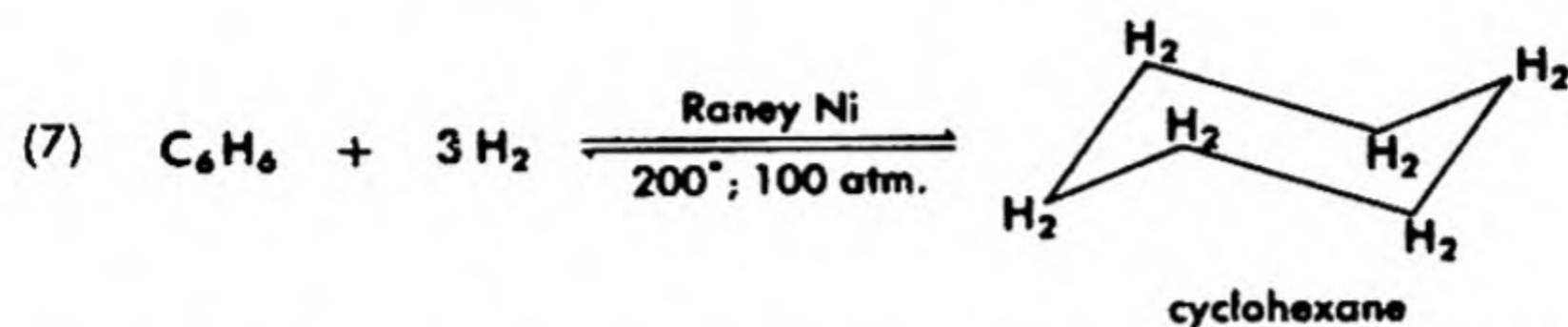
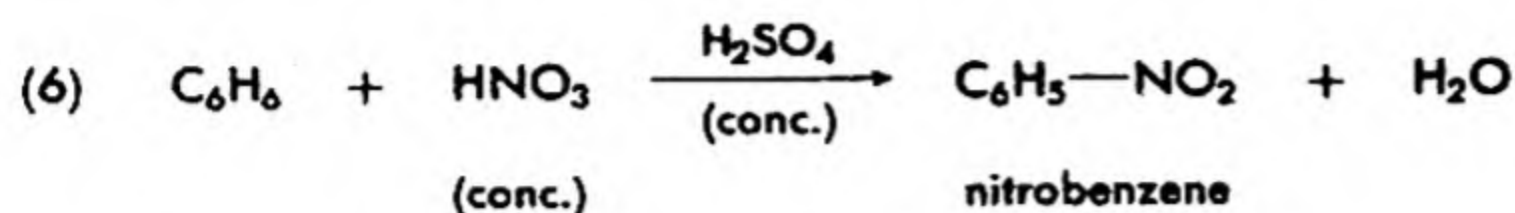
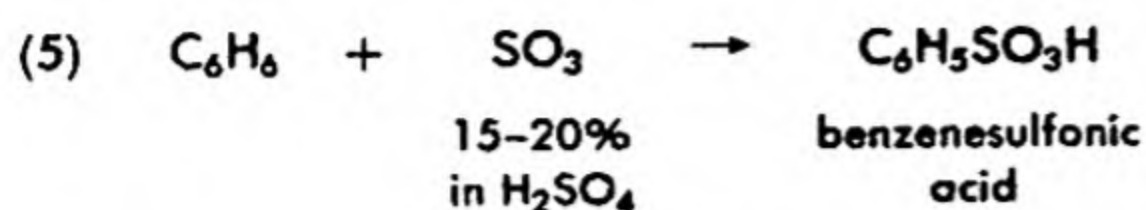
^a Variation due to method of measurement. Relative order of magnitude is always the same for these cases.

The chemical properties of benzene and other arenes are thus explained by the delocalization energy content of the conjugated system. Reactions of benzene must involve the formation of stable enough intermediates to overcome, in part at least, the loss of 36 kcal./mole of aromatic resonance energy. Such reactions lead most frequently to substitution rather than addition, since the latter must result in ultimate destruction of the aromatic resonance and must proceed against a 36 kcal./mole energy disadvantage over similar additions in ethylene.

Once addition has begun, however, a nonaromatic diene has formed, which adds the next two moles of reagent much more easily; these latter stages are energetically similar to addition in ethylene. The consequence is that addition to benzene is often an all-or-nothing reaction; if any addition occurs at all, three moles of reagent add to form a cyclohexane derivative.

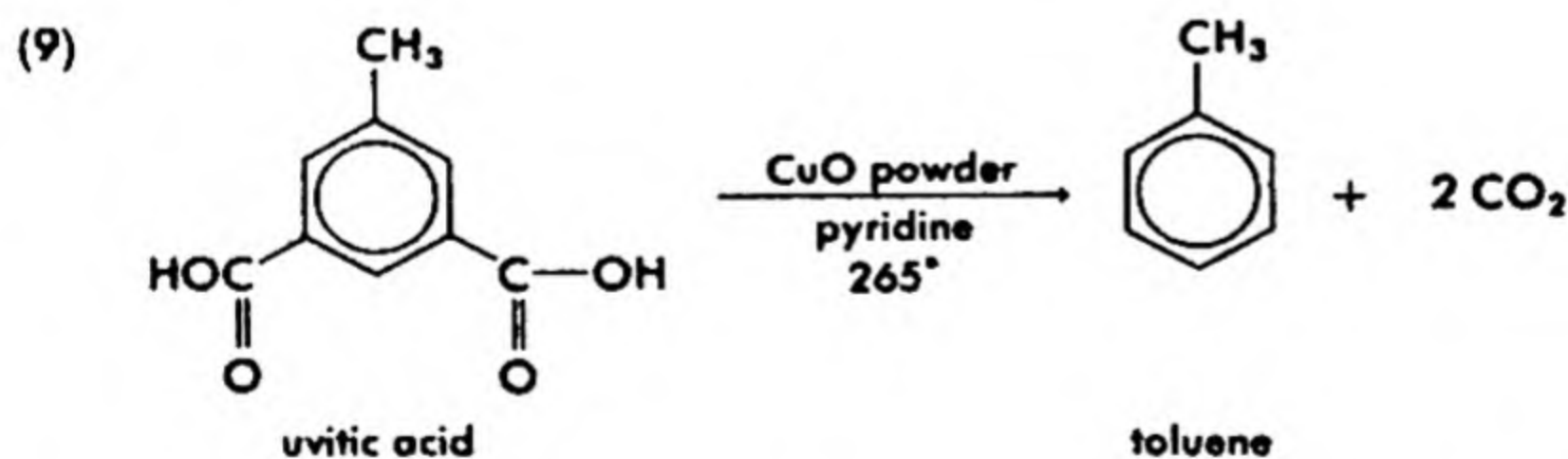
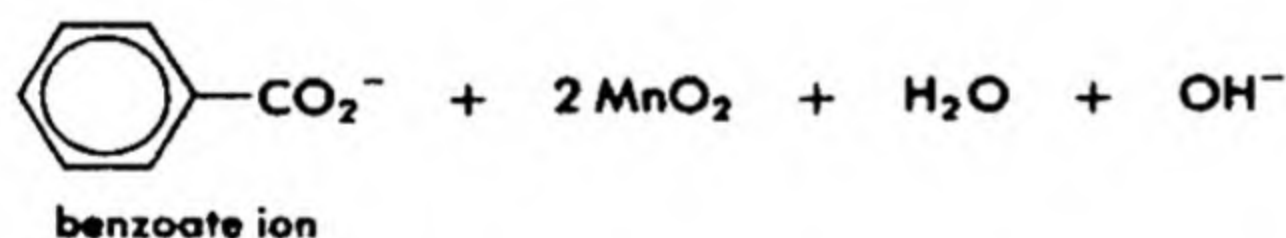
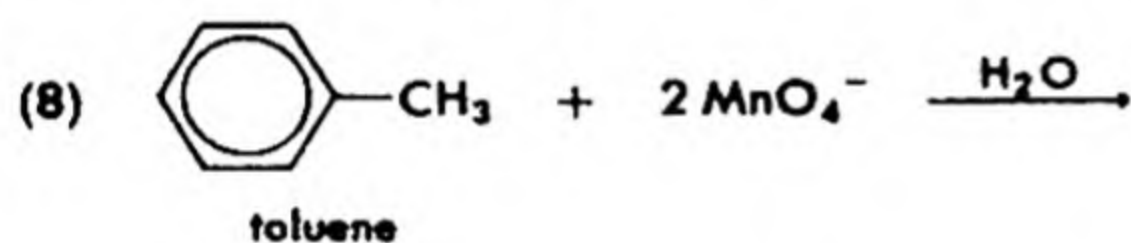
Some examples of typical reactions of benzene are given in the following equations. Note that electrophilic reagents bring about substitution, not addition, in benzene (eqs. (3-5)). Furthermore, both substitution and addition in benzene are usually much slower than additions to olefins.





The hydrogenation reaction (eq. 7) is reversible. Benzene is now prepared commercially from petroleum by dehydrogenation of cyclohexane (and hexane) over a catalyst consisting of platinum on alumina. The process is called reforming (§5-1D, eq. 5).

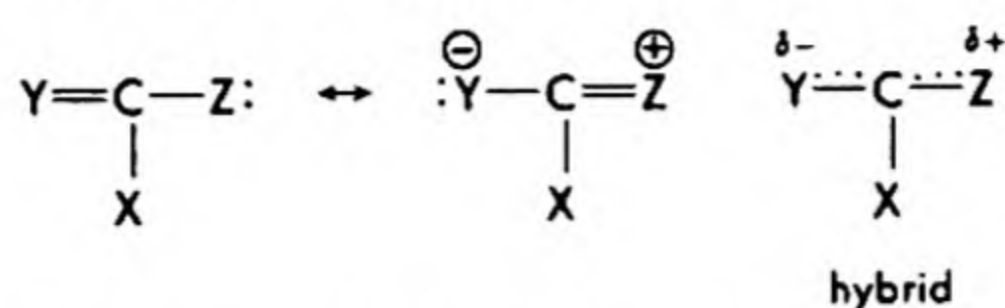
The resistance of the benzene ring to destruction is exemplified in the following oxidation and pyrolysis. Recall, by contrast, the ease of oxidation of olefins (§7-2A).



(2) *Acidity in Phenols and Carboxylic Acids.* Certain open conjugated systems are characterized by considerable resonance stabilization. Thus, compounds with the structure $\text{Y}=\text{C}(\text{X})-\text{Z}$ exhibit electron delocalization

sufficient to provide 15-30 kcal./mole of resonance energy. The valence-bond structures for this type of system show, in general, the incurrance of a partial positive charge on atom Z and a partial negative charge on

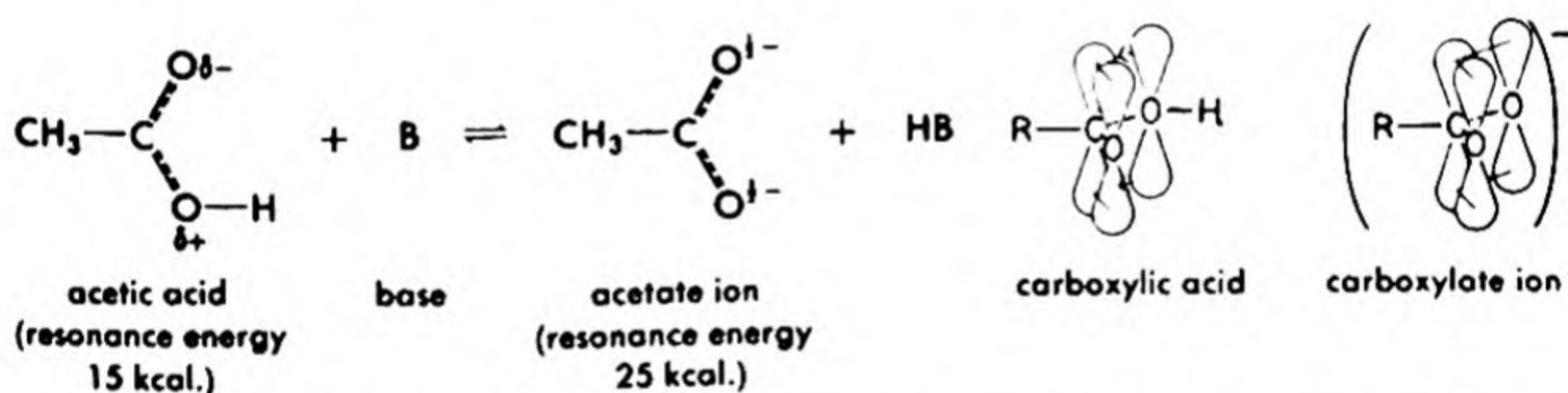
atom Y. Thus greater electronegativity in Y and greater electropositivity in Z increase the resonance energy, since these factors tend to make the



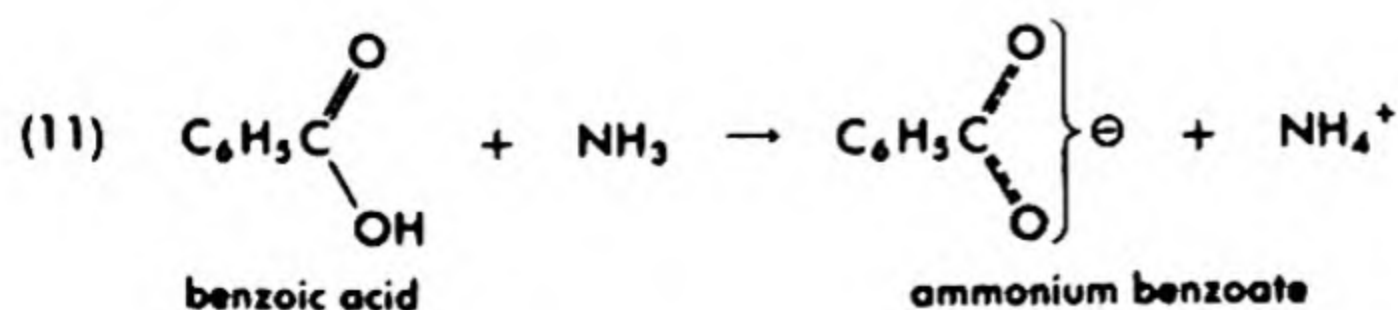
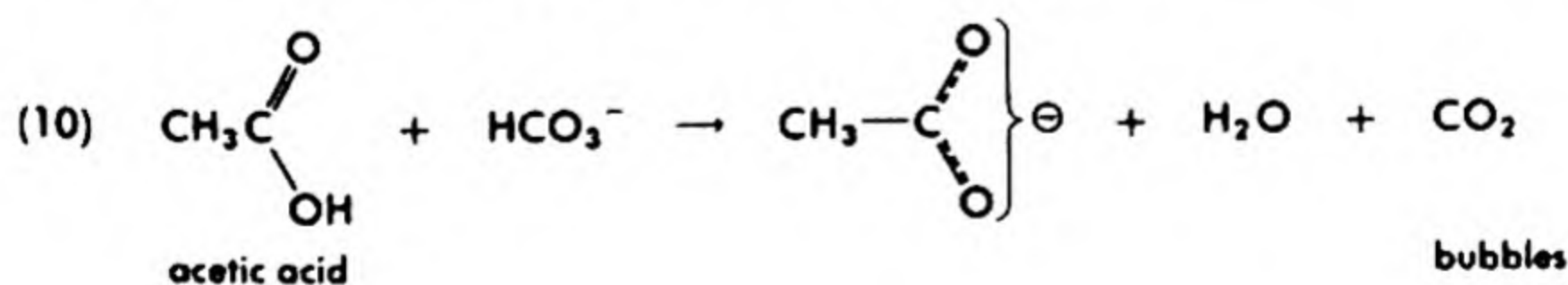
two valence-bond structures energetically more equivalent. The charge-separated structure is usually of higher energy content, hence contributes less to the resonance hybrid.

In the specific system of carboxylic acids, $\text{R}-\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{OH} \end{array}$, the carbonyl

oxygen atom has the role of Y in the general formula, and the hydroxy oxygen atom has the role of Z. Resonance stabilization when R is saturated is about 15 kcal./mole. However, when the proton is removed from the hydroxy group by a base, the resulting carboxylate anion involves two identical structures with charge delocalization (favorable) rather than charge separation (unfavorable), and resonance stabilization is considerably greater (See energy diagrams, Fig. 7-7.)



Consequently, a carboxylic acid such as acetic acid has considerable tendency to ionize ($K_i = 1.8 \times 10^{-5}$) even in a base as weak as water. The acid strength of acetic acid is sufficient to make it react rapidly with bases such as bicarbonate ion, ammonia, or hydroxide ion and slowly in aqueous solution with metals such as zinc and magnesium.



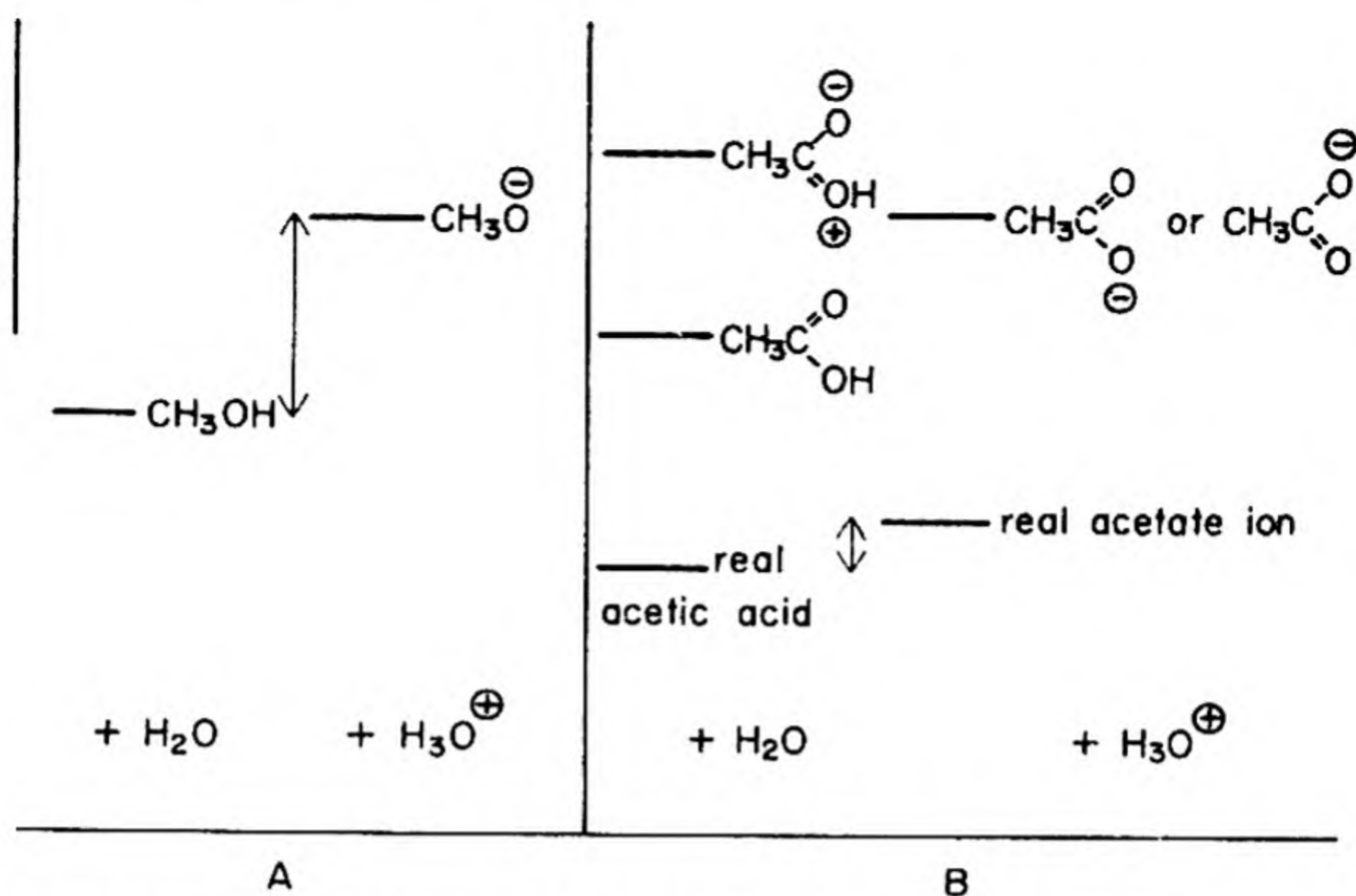
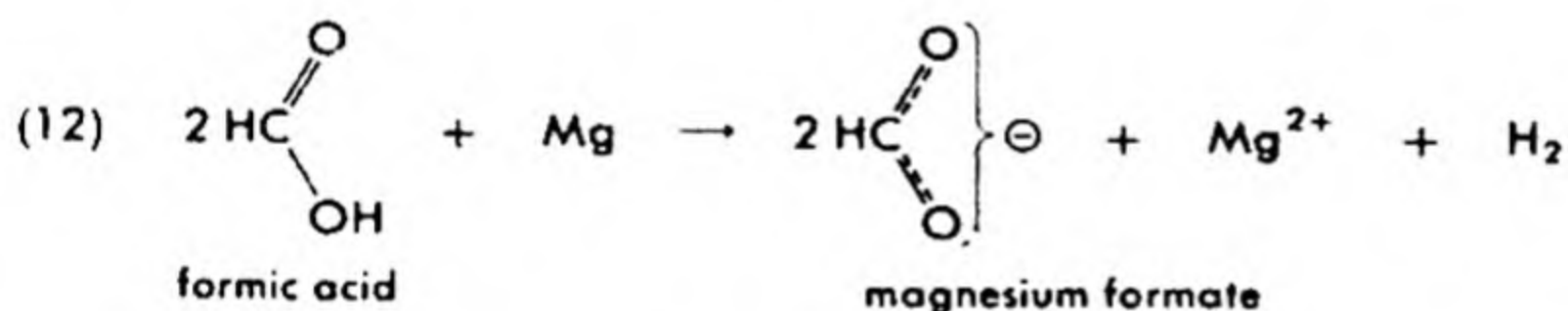
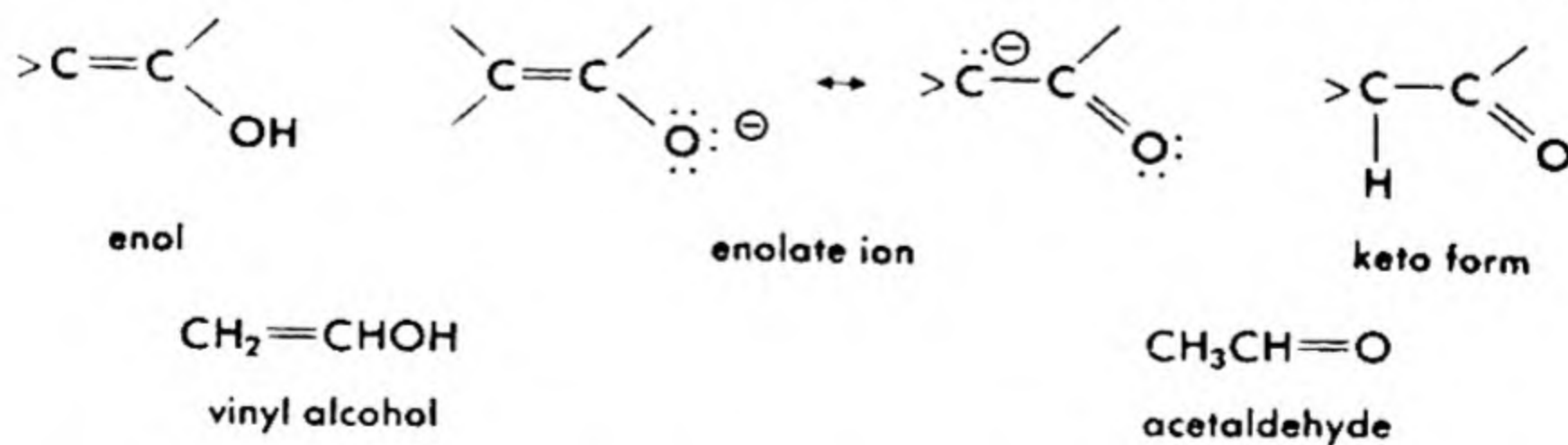


Fig. 7-7. Energy Relationships in Weak Acids and Their Conjugate Anions. (A) Energy diagrams for methanol and methoxide ion, (B) Energy diagrams for acetic acid and acetate ion (arbitrary scales for each).

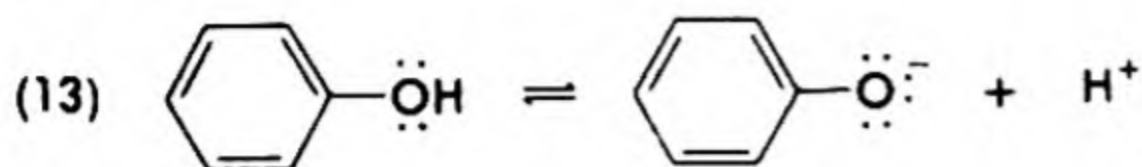


Enols, like carboxylic acids, also are acidic because of the greater resonance stabilization of the enolate ion than of the enol itself. However, most enols are not available for study as they are usually unstable with respect to their keto forms. For example, all preparations designed to lead to vinyl alcohol lead instead to its tautomer, acetaldehyde (see §8-2F).

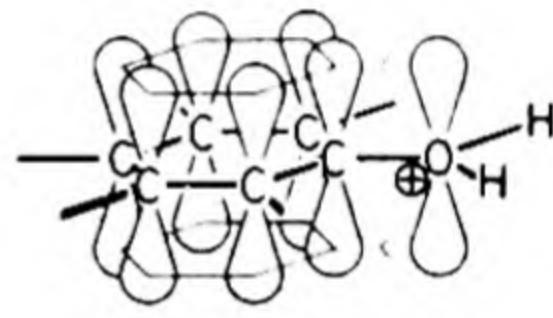
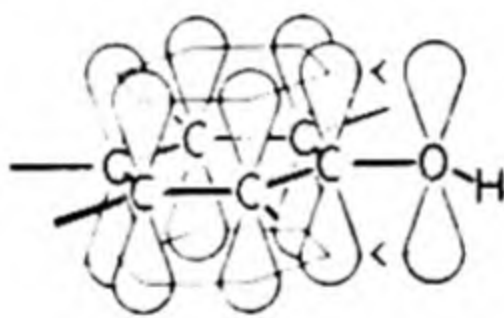
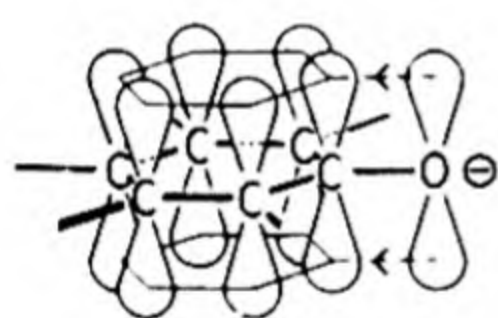
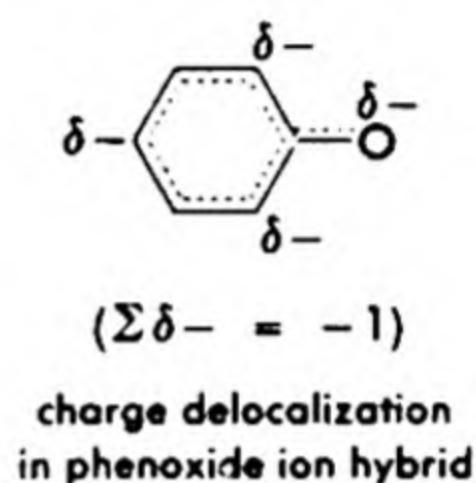
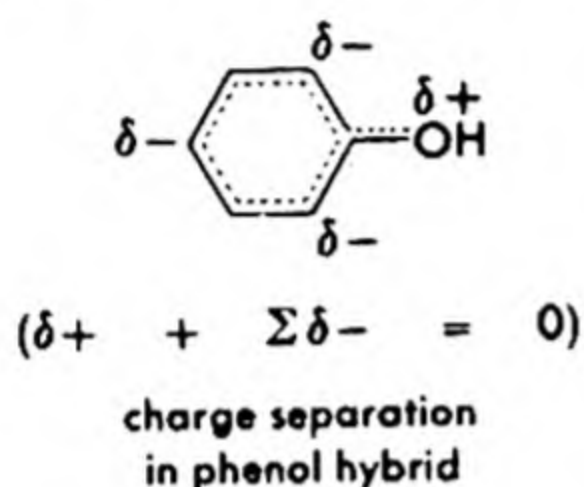


However, if the double bond of the enol is replaced by an aromatic ring, as in phenol, the aromatic ring resonance energy makes the enol form much more stable than the keto form, so that the relative stabilities

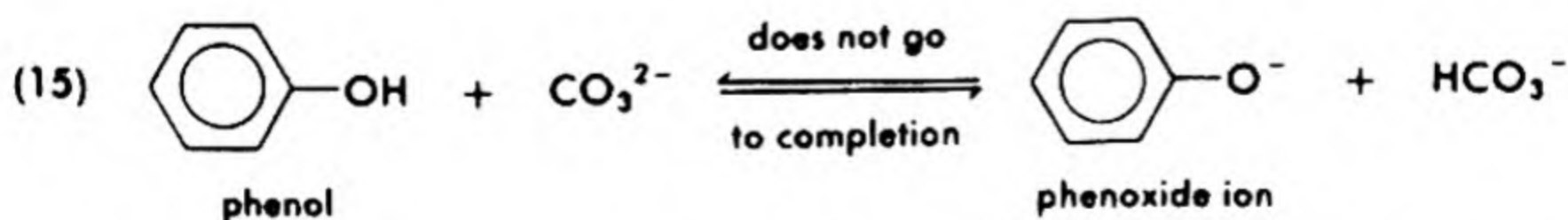
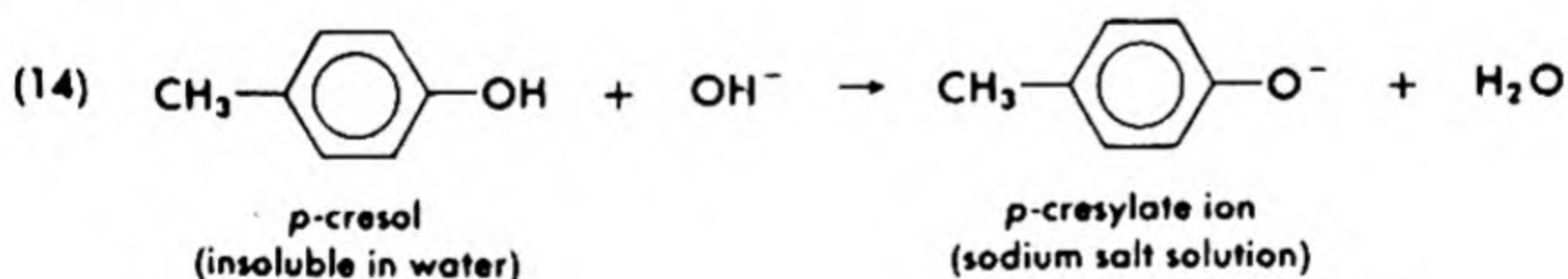
of various phenols and their conjugate bases (aryloxide ions) are measured readily.



Conjugation occurs in both the phenol and the phenoxide ion, but is more effective in the latter, where electron delocalization does not involve charge separation, than in the former, where charge separation is involved. The result is that phenol is a much stronger acid than are alcohols, although it is not as strong as carboxylic acids.



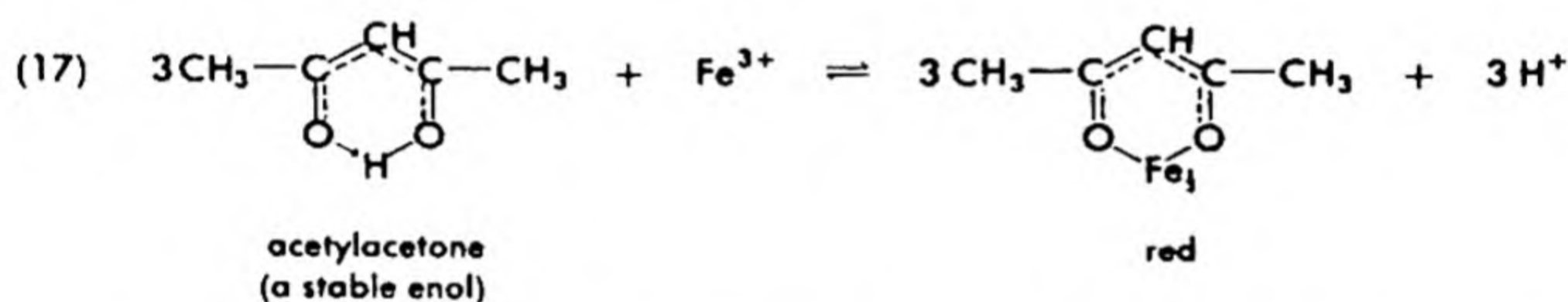
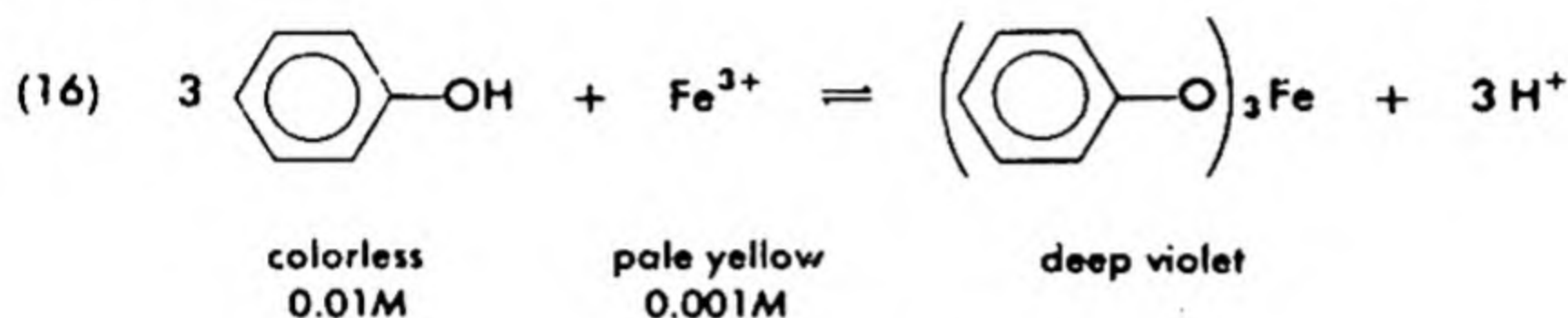
Thus, phenol and phenols in general are strong enough acids to react with strong bases such as hydroxide ion, but not weak bases such as bicarbonate ion. Phenols are about as acidic, in fact, as the bicarbonate ion ($K_i \sim 10^{-11}$).



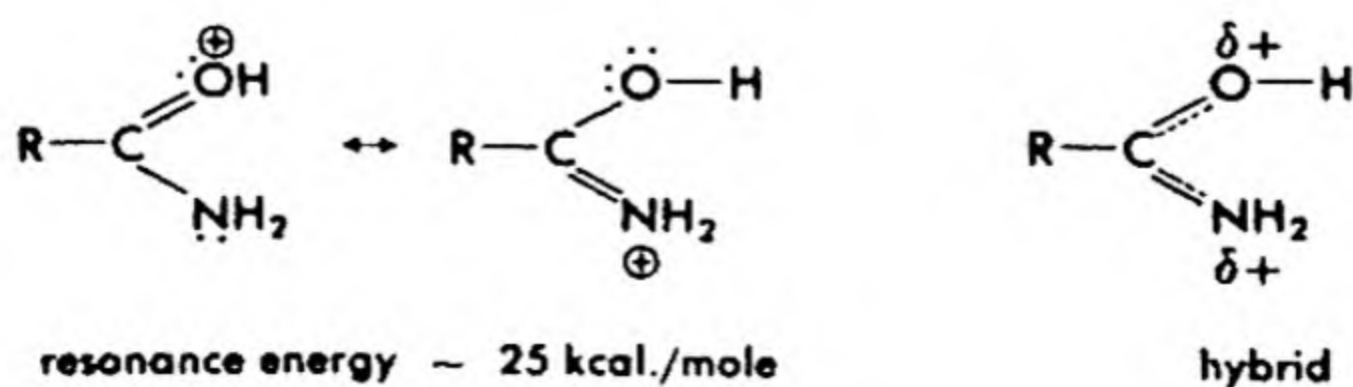
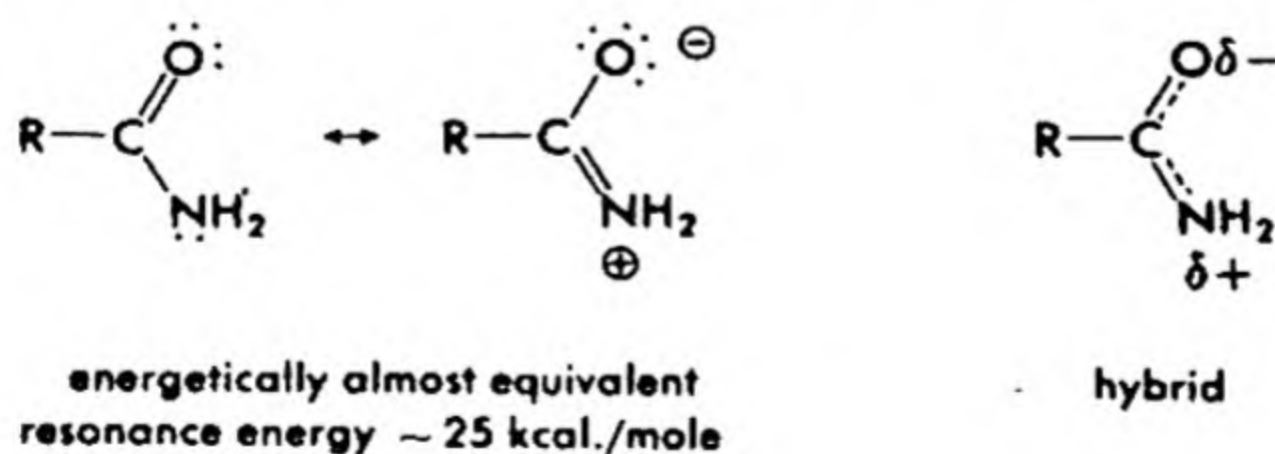
Phenols are thus distinguishable from carboxylic acids in that they do not liberate carbon dioxide gas from bicarbonates as do the latter, and from alcohols in that they generally dissolve completely in aqueous sodium hydroxide, as alcohols which are insoluble in water do not. A few

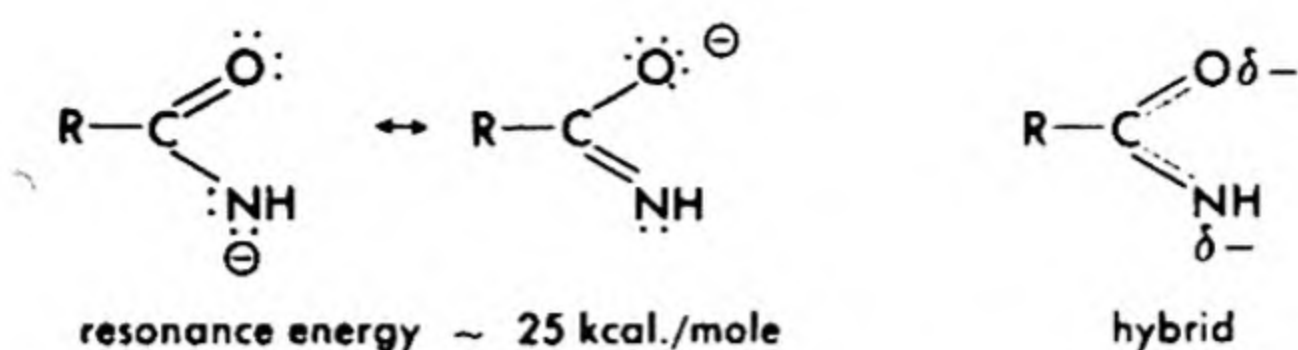
phenols, notably β -naphthol, form sparingly soluble sodium salts, hence react with, but do not dissolve in, sodium hydroxide.

Phenols that are water soluble are not distinguishable from water-soluble alcohols by reaction with aqueous bases. Here, a peculiarity of phenols in reaction with certain transition metal ions is exploited. A very sensitive test, for example, is the formation of deep green, blue, or violet complexes between the phenol and ferric ion. Neither alcohols nor carboxylic acids give intensely colored complexes, but other enols and some other types of compounds do. The equations below are representative, but the products shown are not necessarily the only colored complexes formed.



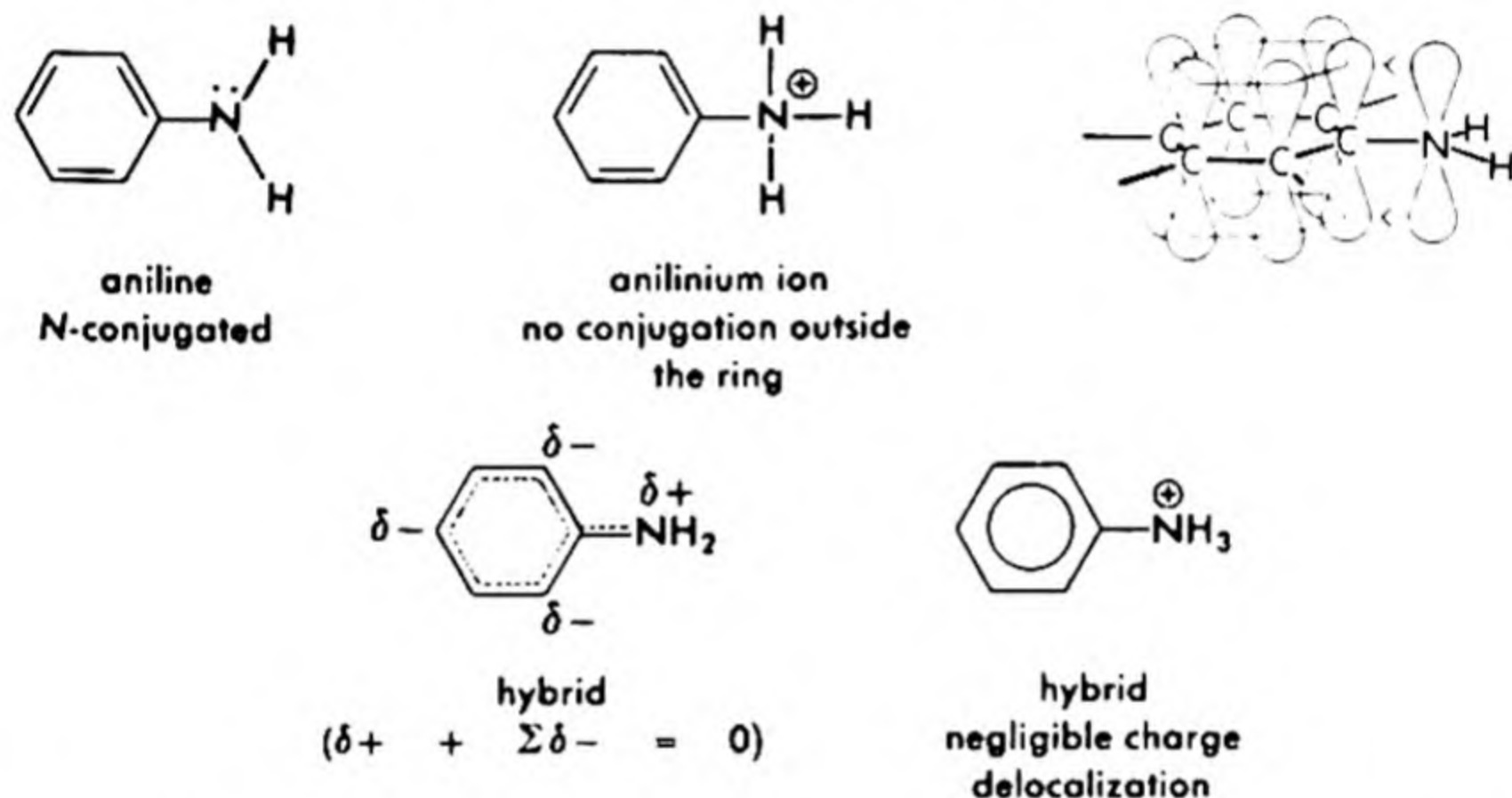
(3) *Basicity in Amides and Arylamines.* Resonance effects are observed in amides, also. Here, the electron-donating ability of the nitrogen atom (as Z, §7-3A(2)) and the electron-accepting ability of the oxygen atom (as Y) combine to stabilize the free amide as much as either the conjugate acid cation or conjugate base anion of the amide.





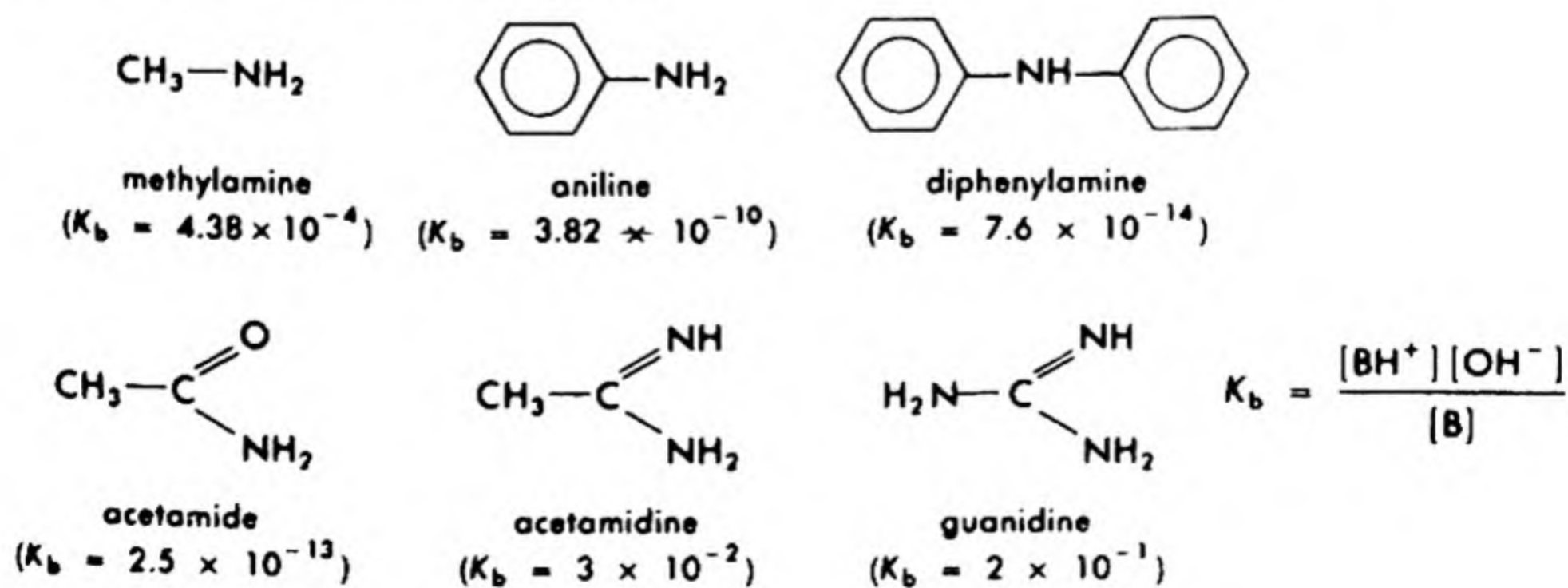
Amides are, therefore, neutral amphoteric compounds which form salts only in very strong acids or very strong bases. It may thus be noted that the amino group in an amide is not as basic as it is in a free amine.

Reasoning analogous to that above for amides and to that earlier discussed for phenols leads to the conclusion that arylamines should be weaker bases than alkylamines, but not as weak as amides. The amino group interacts weakly with the ring to provide some resonance stabiliza-



tion of the free amine as compared with its conjugate cation, which has no resonance interaction between the ammonio group and the ring.

The interaction is less than that with a carbonyl group, as in an amide; thus, an arylamine is not neutral, but not as basic as ammonia. A second phenyl group, however, provides sufficient additional interaction with the amino group to make it neutral.



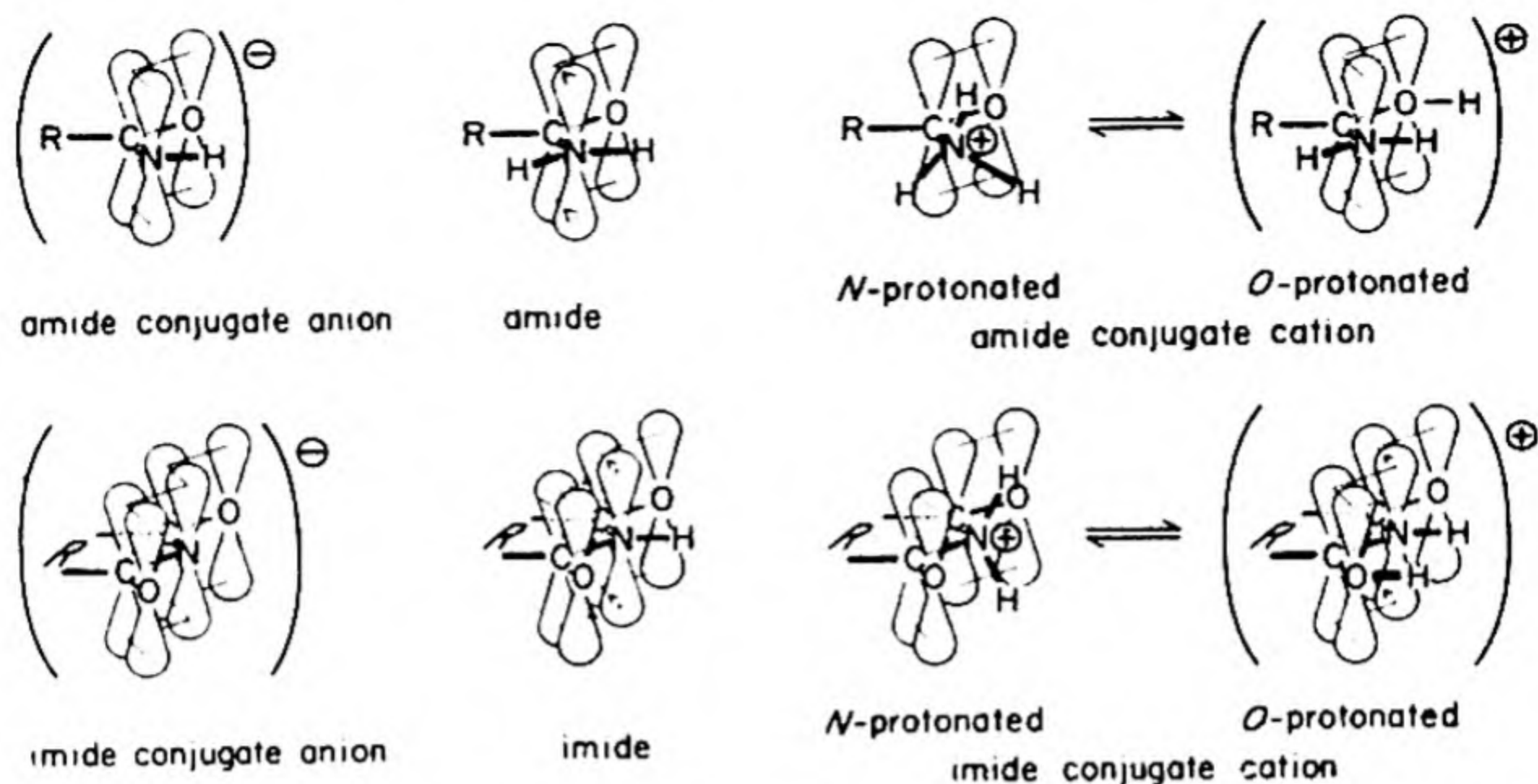
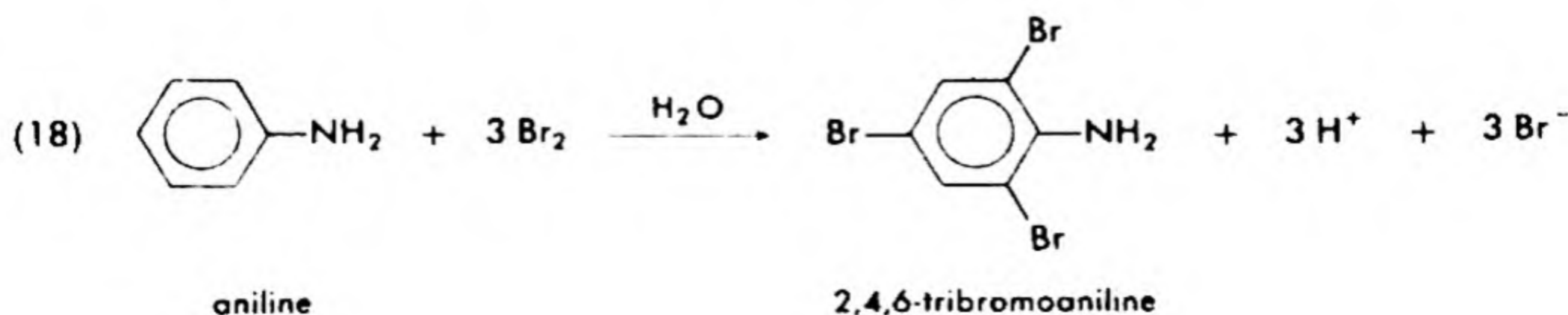
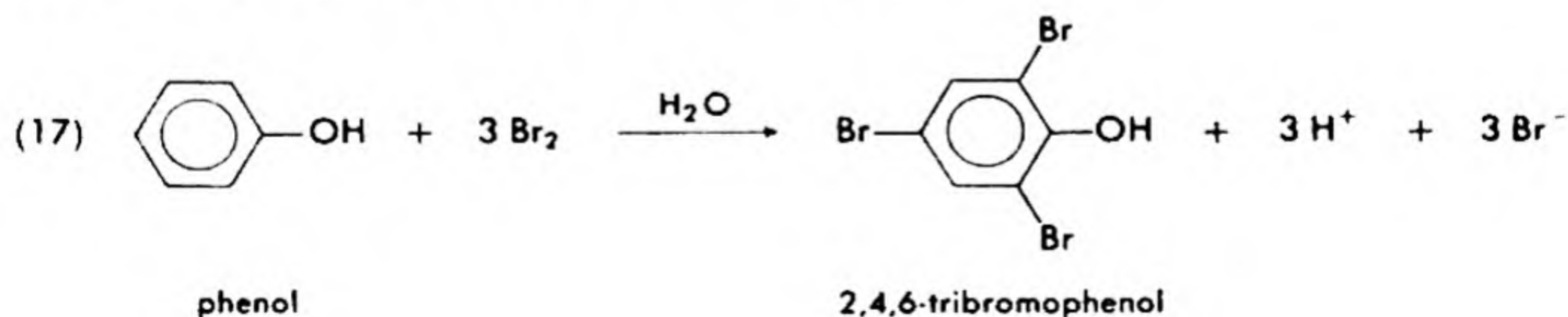


Fig. 7-8. Orbital Formulas for Amide and Imide and Their Conjugate Anions and Conjugate Cations.

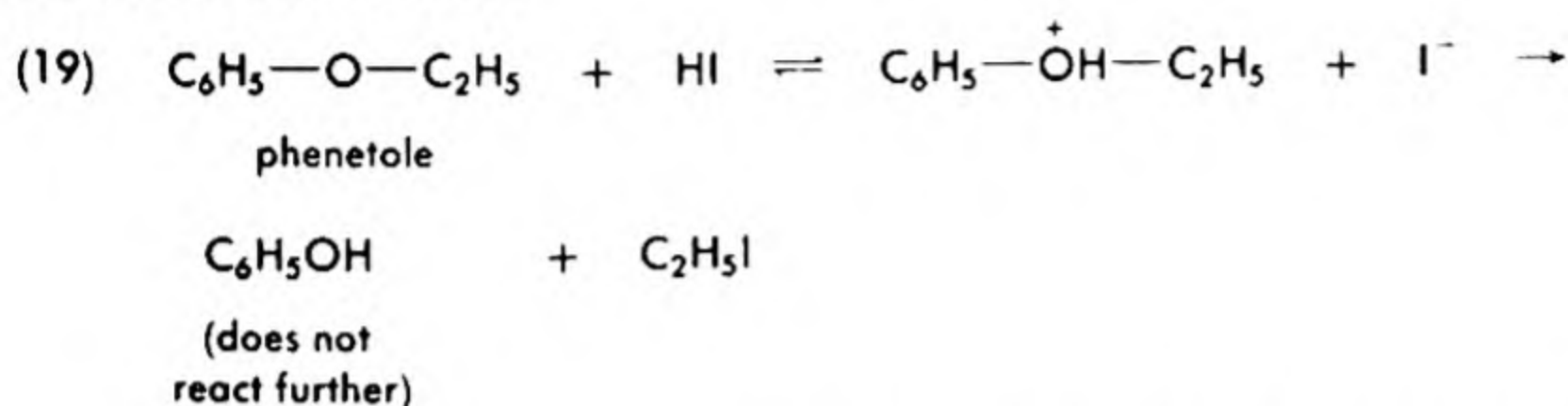
Reasoning such as that in this and the preceding sections can be applied to explain the weakly acidic properties of imides (see Fig. 7-8).

Since interaction between a hydroxy group, as in phenols, or an amino group, as in arylamines, with an aromatic ring greatly influences the properties of these groups, it is to be expected also that the properties of the aromatic ring are equally influenced. The substitution reactions which proceed with moderate ease in benzene, for example, nitration, sulfonation, and halogenation, proceed with great dispatch in phenols. Halogenation likewise occurs rapidly in arylamines, but nitration and sulfonation conditions convert the amines to unreactive arylammonium ions.

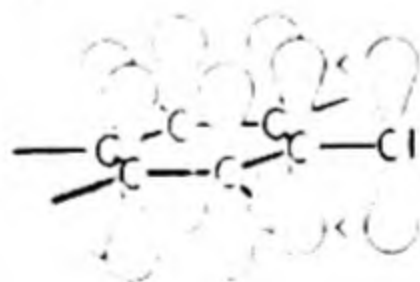
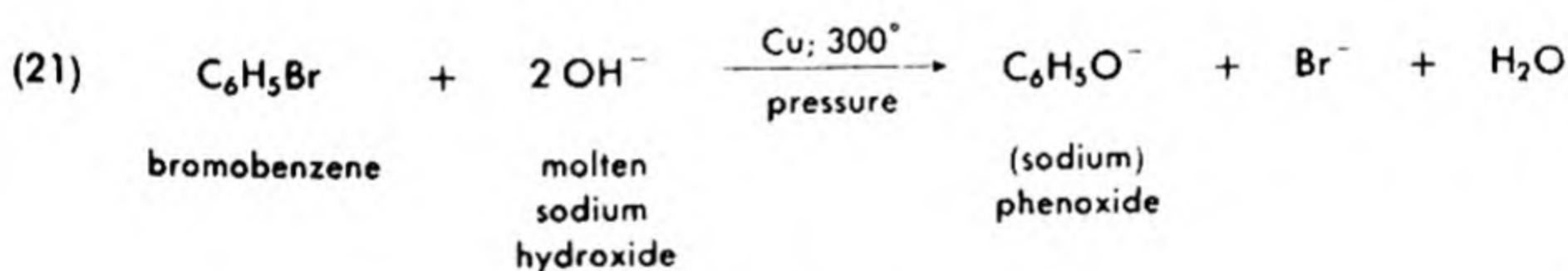
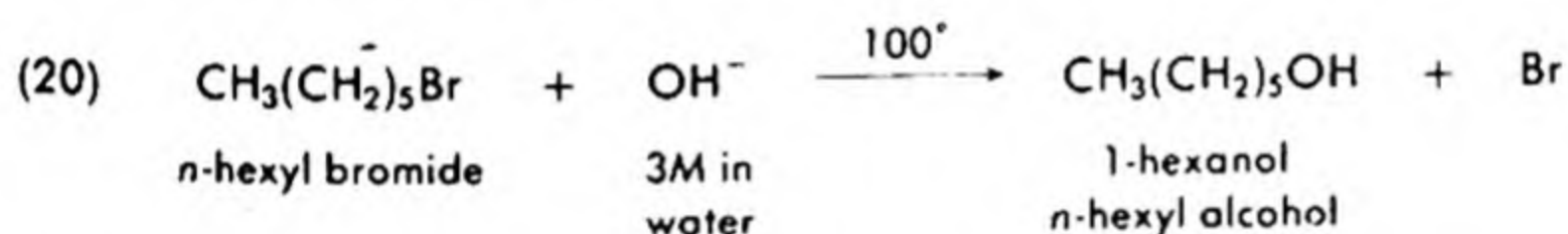
Phenol and aniline, for example, form dense white precipitates as fast as bromine water can be added to them. The ring is tribrominated in the positions *ortho* and *para* to the functional group unless that position is occupied by a group other than a hydrogen atom.



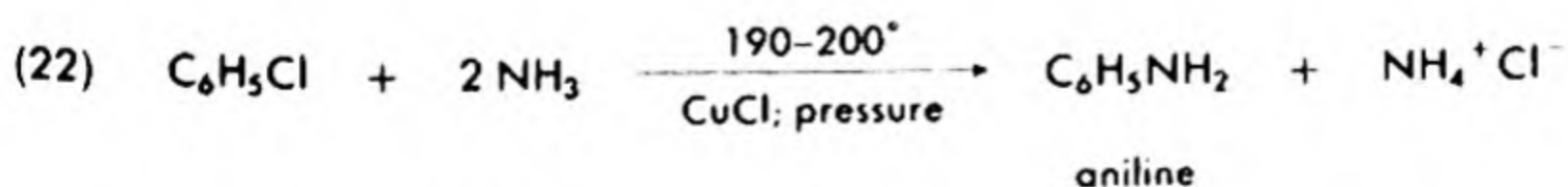
(4) *Carbon-Heteroatom Bonds at Unsaturated Carbon.* It should be apparent from §7-3A(2) that resonance interaction between an oxygen atom and an aromatic ring will strengthen that bond and make it less susceptible to cleavage. This is, in fact, true; treatment of aryl ethers with hydriodic acid cleaves alkyl-oxygen bonds, but not aryl-oxygen. Diphenyl ether does not react.



Halogen atoms, too, participate in conjugation with the aromatic ring. In the absence of groups which provide special effects (discussed in §22-6), aryl-halogen bonds are highly resistant to displacements. This can be seen in the different conditions required for hydrolysis of *n*-hexyl bromide and bromobenzene. In general, aryl halides (without electronegative groups in



addition to halogen) are unsuitable for displacement reactions. Only a few displacements in chlorobenzene are industrially feasible; one is the preparation of phenol via the phenoxide, similar to eq. (21); another is the preparation of aniline, eq. (22). Both, developed by Dow Chemical Company, are called Dow processes.



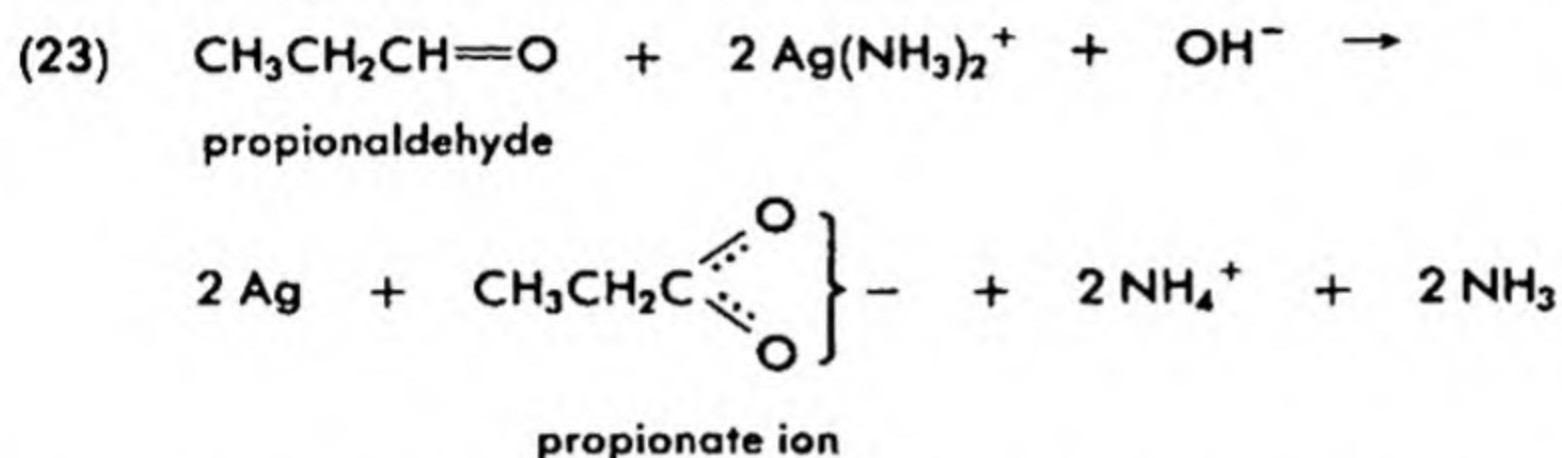
B. Oxidation and Reduction

It was observed (§7-2A) that carbon-hydrogen bonds in aliphatic hydrocarbons are oxidized with difficulty. Although there are several pathways

for oxidation, and thus several ways molecular environment can affect oxidizability, a few types of structure stand out as unusually susceptible.

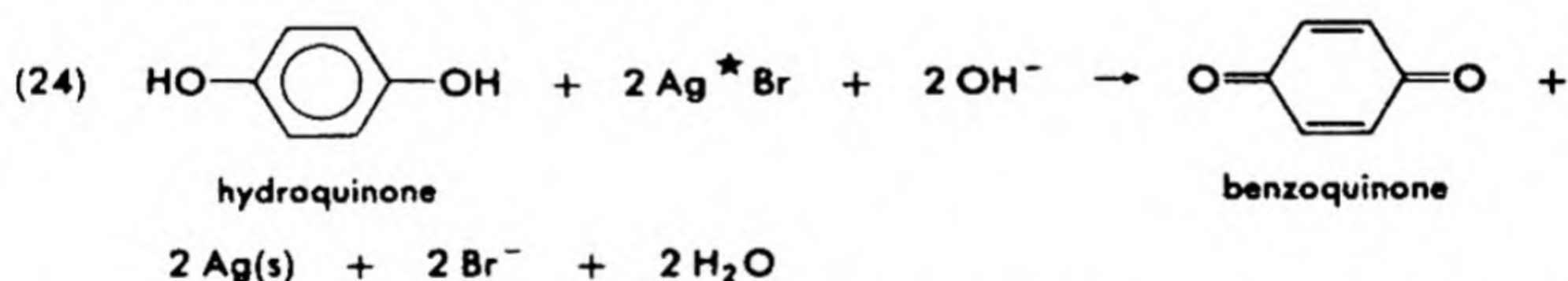
The aldehyde group is one that is remarkable for ease of oxidation by most pathways. This seems all the more remarkable when it is remembered that oxidation is a decrease in electron density, and that the carbonyl group has already assured a low electron density at the aldehyde hydrogen. The explanation lies in the stabilization of the intermediates, which are of several kinds, by resonance involving the carbon-oxygen double bond.

A typical reaction in which the ease of oxidation of an aldehyde is contrasted to the resistance of a ketone is the Tollens' test, which uses the mild oxidizing agent, diamminosilver ion. The formation of a silver mirror on a clean glass surface or a black precipitate of finely divided silver is

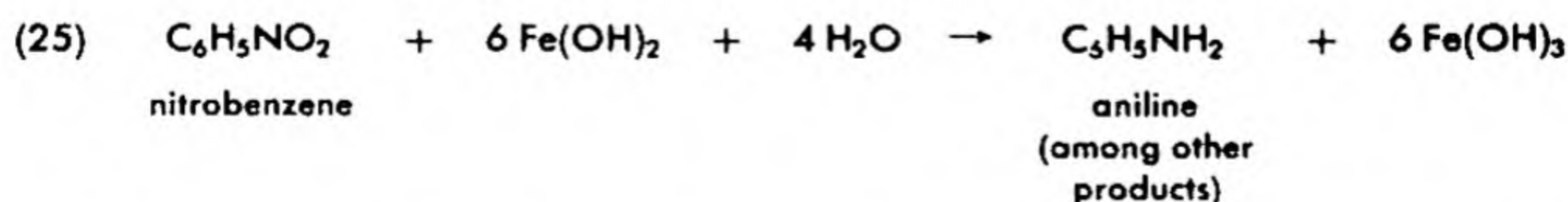


a positive test for an aldehyde (also given by α -hydroxy ketones, aromatic amines, and α -naphthol). Simple ketones do not react.

Hydroquinone and its homologs are easily oxidized to the related quinones, for example, by light-activated silver ions (Ag^\star), a reaction that is used in photographic development.

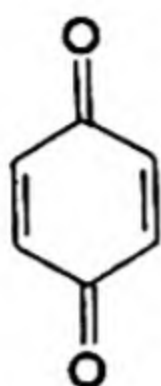
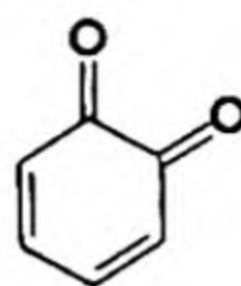


Several classes of organic compounds are moderately strong oxidizing agents. Most of these are compounds with oxidized nitrogen, such as nitro compounds, nitrates, nitrites, and nitroso compounds. All of these are known for their ability to oxidize freshly prepared moist ferrous hydroxide (pale blue-gray) to hydrated ferric oxide (brown).

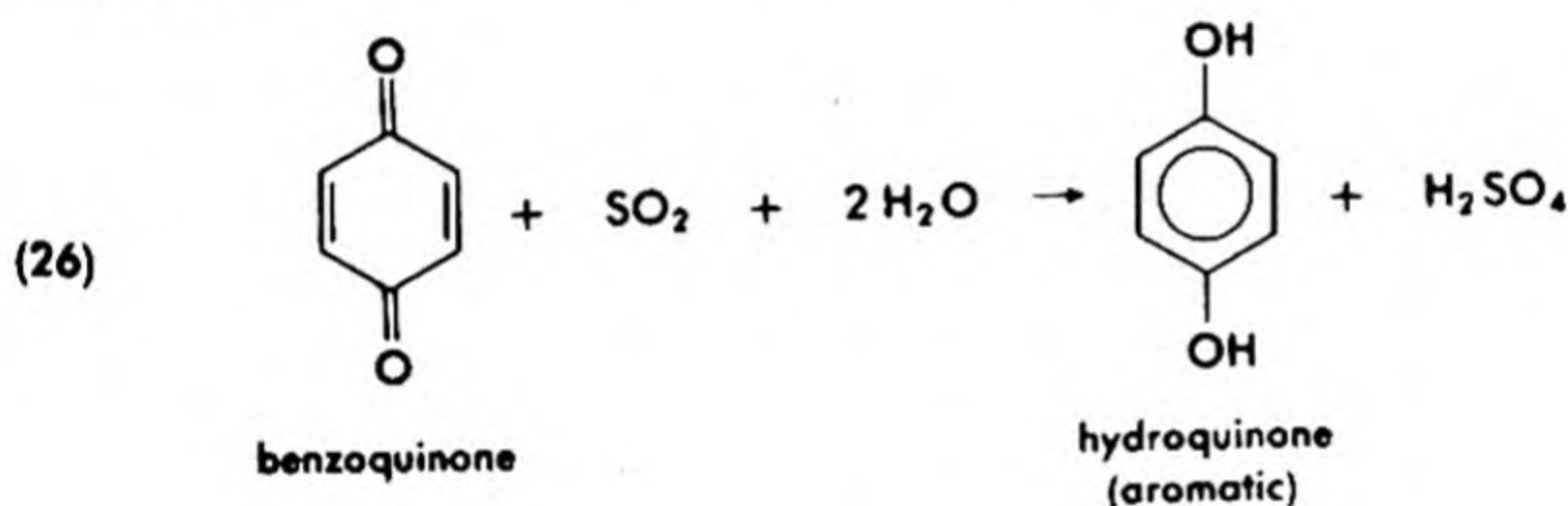


However, one class containing only carbon, hydrogen, and oxygen is also notable for the oxidizing ability of its members. This again is related

to the question of resonance. Quinones do not have an aromatic system; *p*-quinones are doubly cross-conjugated cyclic ketones. *o*-Quinones are linearly conjugated.

*p*-benzoquinone*o*-benzoquinone

Both form aromatic systems upon reduction. The stabilization by aromatic resonance makes the hydroquinones and pyrocatechols the preferred products in redox equilibria. Thus, such mild reducing agents as sulfurous acid and ferrous hydroxide easily reduce quinones to the aromatic diols.



SUPPLEMENTARY READINGS

- Herz, W., *The Shape of Carbon Compounds*, Benjamin, New York, 1963, Chapter IX.
- Meislich, H., "Rules for Molecular Orbital Structures," *J. Chem. Educ.* **40**, 401-408 (1963).
- VanderWerf, C. A., *Acids, Bases and the Chemistry of the Covalent Bond*, Reinhold, New York, 1961, Chapters 3 and 4.
- Waack, R., "The Stability of the 'Aromatic Sextet'," *J. Chem. Educ.* **39**, 469-472 (1962).

QUESTIONS AND PROBLEMS

1. Write equations for those of the following implied reactions which occur, with conditions. If the compounds do not react under mild conditions, write NR.

- | | |
|---|--|
| a. $\text{C}_6\text{H}_6 + \text{Br}_2 \rightarrow$ | d. $\text{C}_6\text{H}_5\text{OH} + \text{Br}_2 \rightarrow$ |
| b. $\text{C}_6\text{H}_6 + \text{H}_2\text{SO}_4 \rightarrow$ | e. $\text{C}_6\text{H}_5\text{OH} + \text{NaOH} \rightarrow$ |
| c. $\text{C}_6\text{H}_6 + \text{HCl} \rightarrow$ | f. $\text{C}_6\text{H}_5\text{OH} + \text{HCl} \rightarrow$ |

2. Show how the following compounds can be distinguished by simple chemical

tests. Describe the observed differences in results of each test. Write equations for any reactions that occur.

- | | |
|--|---|
| a. benzene, hexane, and 2-methyl-2-pentene | i. benzoic acid and <i>p</i> -cresol |
| b. 1-hexanol and phenol | j. salicylic acid and resorcinol |
| c. <i>p</i> -dichlorobenzene and phenol | k. salicylic acid and benzoic acid |
| d. <i>p</i> -cresol and cyclohexanol | l. acetic anhydride and propionic acid |
| e. propionaldehyde and acetone | m. <i>m</i> -toluidine and <i>m</i> -cresol |
| f. benzaldehyde and benzoquinone | n. toluene and nitrobenzene |
| g. benzoic acid and benzaldehyde | o. benzaldehyde and nitrobenzene |
| h. acetic acid and isobutyl alcohol | p. benzoquinone and nitrobenzene |

3. Write equations for any reactions that occur in the following mixtures of substances under moderate conditions. Use structural formulas. Indicate essential special conditions. If no reaction occurs, write the formulas of the reagents and NR.

- | | |
|---|--|
| a. <i>p</i> -xylene + nitric acid | n. sodium butanoate solution + calcium chloride solution |
| b. toluene + sodium hydroxide | o. sodium benzoate solution + dilute hydrochloric acid |
| c. chlorobenzene + sodium hydroxide | p. propionic acid + water |
| d. <i>o</i> -cresol + sodium hydroxide | q. acrylic acid + dilute sodium hydroxide |
| e. α -naphthol + sodium bicarbonate | r. aniline + water |
| f. <i>m</i> -cresol + hydrochloric acid | s. aniline + dilute hydrochloric acid |
| g. isobutyraldehyde + Tollens' reagent | t. <i>p</i> -toluidine + dilute sodium hydroxide |
| h. acetone + Tollens' reagent | u. phthalimide + dilute sodium hydroxide |
| i. propionaldehyde + acidic potassium dichromate solution | v. nitrobenzene + ferrous hydroxide |
| j. butanone + acidic potassium dichromate solution | w. acetone + ferrous hydroxide |
| k. propionic acid + sodium bicarbonate solution | x. benzoquinone + ferrous hydroxide |
| l. formic acid + acidic potassium dichromate solution | |
| m. <i>n</i> -valeric acid + sodium chloride | |

4. What does the term aromatic imply regarding an organic compound?
5. Is it correct to say that benzene is saturated? Why?
6. A student obtained 28.7 g. of product from the mononitration of 30.0 g. of benzene. Write the equation for the reaction, indicating conditions. Calculate the per cent yield of product.
7. In each lettered statement below the behavior of a hydrocarbon is described. Characterize the compound in as much detail as the evidence warrants.
 - a. A hydrocarbon does not react with bromine when kept dark. It is insoluble in fuming sulfuric acid.
 - b. A hydrocarbon gives a gray precipitate when mixed with ammoniacal silver nitrate solution.

c. A hydrocarbon decolorizes bromine in carbon tetrachloride without the evolution of fumes. It does not react with potassium permanganate solution.

d. A hydrocarbon reacts slowly with bromine in carbon tetrachloride in the presence of light, more rapidly when iron is added. The hydrocarbon dissolves in fuming sulfuric acid, but not in cold concentrated sulfuric acid.

8. Each compound to be prepared can be made in one step from the suggested starting material. Write equations for the required reactions, including necessary special conditions. Use structural formulas for organic compounds.

- | | |
|---|--|
| a. benzene from cyclohexane | j. butyric acid from the suitable aldehyde |
| b. nitromesitylene from the suitable hydrocarbon | k. carbon dioxide from formaldehyde |
| c. <i>p</i> -toluenesulfonic acid from the suitable hydrocarbon | l. sodium acetate from cheap, readily available starting materials |
| d. benzyl bromide from toluene | m. benzenesulfonic acid from benzene |
| e. sodium phthalate from <i>o</i> -xylene | n. aniline by a Dow method |
| f. sodium phenoxide from chlorobenzene | o. α -nitronaphthalene from naphthalene |
| g. sodium 4-ethylphenoxide from 4-ethylphenol and the cheapest inorganic reagent usable | p. caprylic acid from the suitable alcohol |
| h. quinone from hydroquinone | |
| i. acetone from the suitable alcohol | |

9. What type of reaction is most characteristic of alkyl halides? Why is this not true of simple aryl halides?

10. Write all of the valence-bond structures of phenanthrene and anthracene which do not involve charge separation. Explain qualitatively from these structures why phenanthrene has a higher resonance energy than anthracene.

11. A solid with a pronounced odor is suspected of being an arene or a phenol. What test will quickly and easily show which the compound is? Describe the observations.

12. Tell all that is shown about the structure of the compound which behaves as described in each lettered statement below.

a. A compound reacts with sodium to give a gas. It does not react with sodium hydroxide and contains no halogen.

b. A compound gives a positive test in elementary analysis for halide. It reacts slowly with sodium metal, but does not give a gas. The Baeyer test is negative. The compound is soluble in fuming sulfuric acid.

c. A compound insoluble in water dissolves in dilute sodium hydroxide. The compound does not react with sodium bicarbonate solution. Treatment with bromine water forms a heavy white precipitate.

d. A compound reacts slowly with bromine in sunlight, but does not react with fuming sulfuric acid. After fusion with sodium, a sample of the compound gives a solution that yields no precipitate after dilute nitric acid and dilute silver nitrate are added.

e. A compound soluble in water gives a deep blue color with ferric chloride solution.

f. A compound reacts slowly with hot, concentrated hydrobromic acid. It does not react with sodium. The compound reacts with cold concentrated sulfuric acid to give water-soluble products. The compound gives negative tests for halogen in elementary analysis.

g. A liquid gives a white precipitate with phenylhydrazine and a black precipitate with Tollens' reagent. The compound contains no nitrogen.

h. A solid gives a new solid upon treatment with hydroxylamine, but no reaction with Tollens' reagent. After treatment of the original solid with aqueous sulfur dioxide, its product gives a deep color with ferric chloride solution.

i. A compound insoluble in dilute acid or base dissolves in concentrated sulfuric acid. The compound reacts rapidly with bromine in carbon tetrachloride without giving fumes. It decolorizes acidic potassium permanganate. The compound gives negative results with sodium and with phenylhydrazine. Its elementary analysis shows no sulfur or halogen.

j. A compound soluble in cold, concentrated sulfuric acid does not react with dilute acid or base, sodium metal, potassium permanganate, or hydroxylamine. It reacts only slowly with bromine in carbon tetrachloride. The solution in sulfuric acid gives the original compound upon dilution.

k. A lachrymatory oil reacts with dilute sodium bicarbonate to give a gas, and with ethanol to give a product with a fruity fragrance. The compound does not react with aqueous silver nitrate acidified with nitric acid, either before or after sodium fusion.

l. A pungent liquid reacts with dilute sodium bicarbonate to give a gas. It does not react with ethanol until heated with a little concentrated sulfuric acid, after which it gives a sweet-smelling oil. The original liquid does not react with ferric chloride solution.

m. A white solid insoluble in water reacts with bromine water to give a dense white precipitate. It does not react with sodium bicarbonate, but is soluble in dilute sodium hydroxide solution. Elementary analysis shows sulfur to be absent.

n. A lachrymatory oil reacts with dilute sodium bicarbonate solution to give a gas. It reacts rapidly with ethanol to give a fragrant oil. The compound gives an immediate precipitate when treated with aqueous silver nitrate solution.

o. A compound dissolves slowly in water and somewhat more rapidly in dilute sodium hydroxide solution. Added to ethanol, the compound produces heat and a fragrant oil. No precipitate is formed when the compound is shaken with alcoholic silver nitrate solution.

13. Explain the lack of carbonyl group properties in carboxylic acids. Compare with the lack of olefin properties in benzene.

14. How do the structure and consequent properties of formic acid differ from all other alkanolic acids? How would oxalic acid compare in properties to other alkanedioic acids? Explain the bases of your answers.

15. Arrange the following compounds in order of increasing acid strength from left to right. Benzoic acid, 1-hexanol, carbonic acid, phenol, sulfuric acid, aniline.

16. Three compounds, I, II, and III, were found on the stock shelf in unlabeled bottles. All three were soluble in concentrated sulfuric acid and all three reacted vigorously with sodium to give a gas. I was soluble in dilute sodium hydroxide

solution, but not sodium bicarbonate solution. II was soluble in dilute sodium hydroxide and reacted with dilute sodium bicarbonate to give a gas. III was insoluble in both dilute sodium hydroxide and dilute sodium bicarbonate solutions. None of the compounds gave a test for sulfur.

a. To what class of compound does each belong?

b. Describe what should be expected to happen if 1% ferric chloride solution were dropped into mixtures of each of the compounds in water, assuming them to be monofunctional.

17. Write equations, using specific examples, for three different ways to distinguish between an aliphatic aldehyde and an aliphatic acid by simple chemical tests.

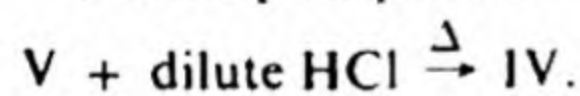
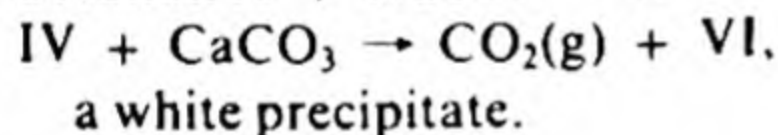
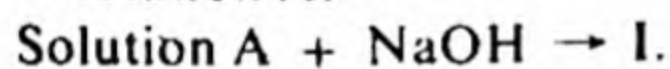
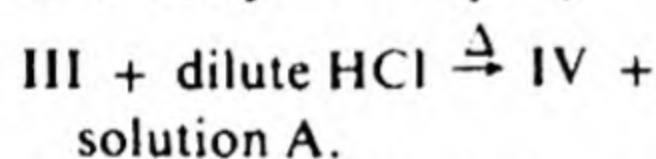
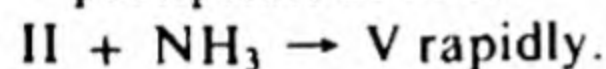
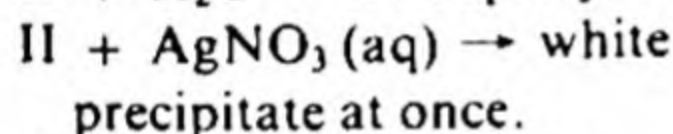
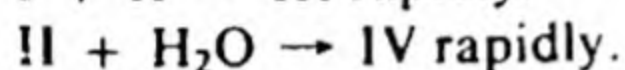
18. Show how to distinguish between an alcohol, a phenol, and a carboxylic acid by simple chemical tests.

a. Assume all to be water-soluble.

b. Assume all to be water-insoluble.

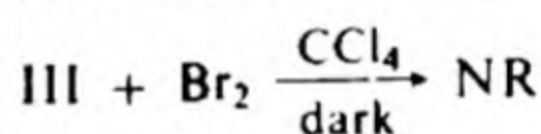
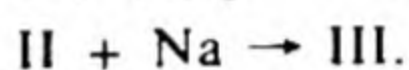
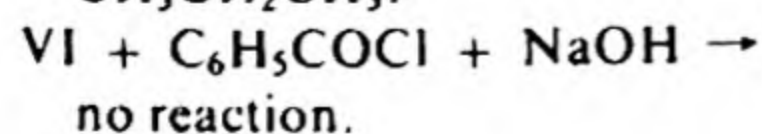
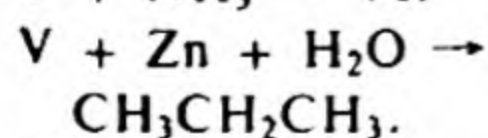
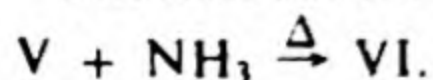
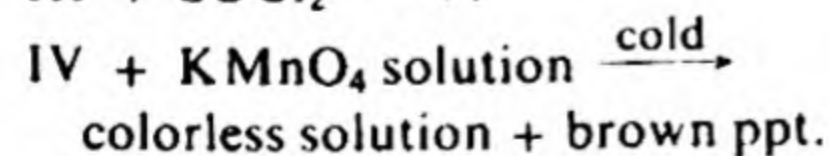
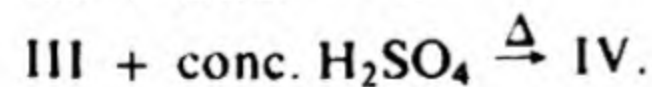
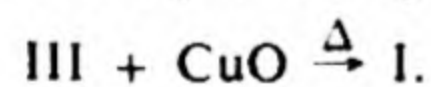
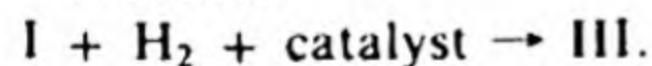
19. Tell all that is shown about the structures of the compounds represented by Roman numerals below. If specific compounds are identified, write structural formulas for them.

a. I dissolves in dilute HCl, but not in pure water.

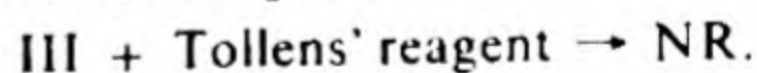
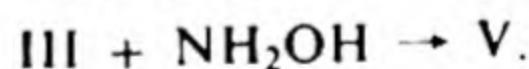
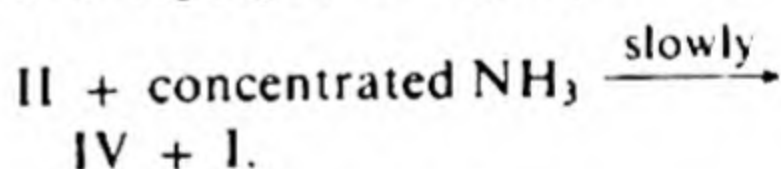
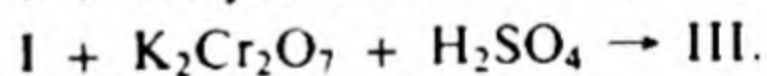


b. I + hydroxylamine \rightarrow II.

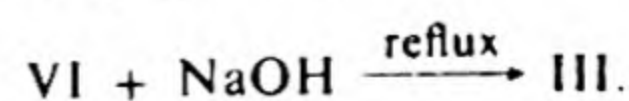
I + Tollens' reagent \rightarrow no reaction.



d. I + acetyl chloride \rightarrow II.



e. I is an oil insoluble in water.



- f. $I + \text{NaHCO}_3 \rightarrow II + \text{CO}_2(\text{g})$
 $I + III + \text{H}_2\text{SO}_4 \rightarrow IV$.
 $I + \text{SOCl}_2 \rightarrow V$.
 $II + V \rightarrow VI$.
 $III + V \rightarrow IV$.
 $III + VI \rightarrow IV + I$.
 $IV + \text{NH}_3 \rightarrow VII$ after a long time.
 $V + \text{NH}_3 \rightarrow VII$ very rapidly.
 $VI + \text{NH}_3 \rightarrow VII$ rapidly.
 $VI + \text{H}_2\text{O} \rightarrow I$.

- g. I is slightly soluble in water.
 $I + \text{dilute NaOH} \rightarrow \text{NH}_3(\text{g})$.
 $I + \text{dilute HCl} \rightarrow II$.
 $I + \text{P}_2\text{O}_5 \rightarrow III$.
 $II + \text{NaHCO}_3 \text{ solution} \rightarrow \text{CO}_2(\text{g})$.

- $II + \text{SOCl}_2 \rightarrow IV$.
 $III + \text{dilute NaOH} \rightarrow \text{NH}_3(\text{g})$.
 $III + \text{H}_2 + \text{Pt} \rightarrow V$.
 $IV + \text{NH}_3 \rightarrow I$.
V is insoluble in water, soluble in dilute HCl.
 $V + \text{Zn powder} \xrightarrow{\Delta} \text{CH}_3(\text{CH}_2)_4\text{CH}_3$.

- h. $I + 2,4\text{-dinitrophenylhydrazine} \rightarrow II$.
 $I + \text{Tollens' reagent} \rightarrow \text{silver mirror}$.
 $I + \text{H}_2 + \text{Pt} \rightarrow III$.
 $III + \text{HNO}_3 \xrightarrow{\text{H}_2\text{SO}_4} IV$.
 $IV + \text{Zn} + \text{HCl} \rightarrow III$.

20. Compare amides with alcohols, amines, and carboxylic acids in respect to acidity and basicity.

21. Explain why imides are acidic.

22. Compare the structures $\text{H}-\text{C}\equiv\text{N}$ and $\text{R}-\text{C}\equiv\text{N}$ as a basis for neutral properties of $\text{R}-\text{C}\equiv\text{N}$.

8

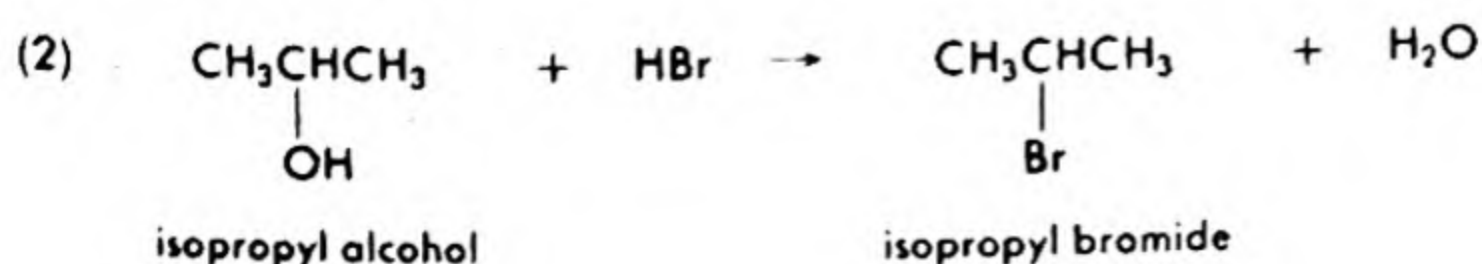
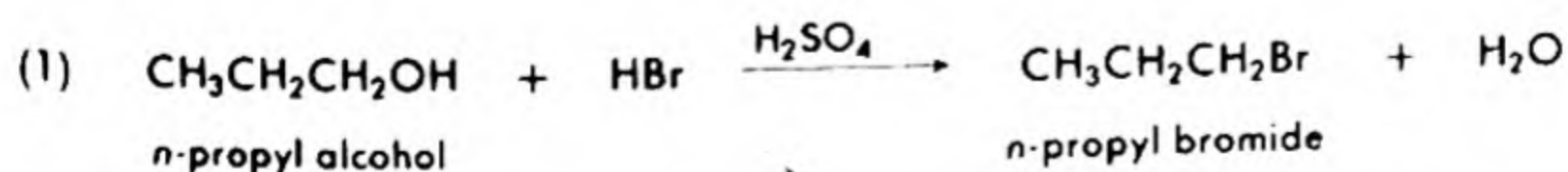
Classical Methods for the Determination of Structure

8-1. PRINCIPLES OF STRUCTURAL PROOF

Determination of the structure of an organic compound depends on direct evidence such as synthesis and analysis, plus corroboration by indirect evidence such as physical properties. Those constitutive physical properties introduced in Chapter 9 and discussed more fully in Unit IV are usually more convenient and sometimes more effective, in combination, than the chemical methods. Nevertheless, the physical methods are based on studies of large numbers of compounds whose structures were elucidated by classical chemical methods in the nineteenth century. Also, in the field of natural products, many compounds are so complex as to require chemical elucidation as well as physical. Therefore, it is still important for the organic chemist to have an appreciation for classical proof of structure.

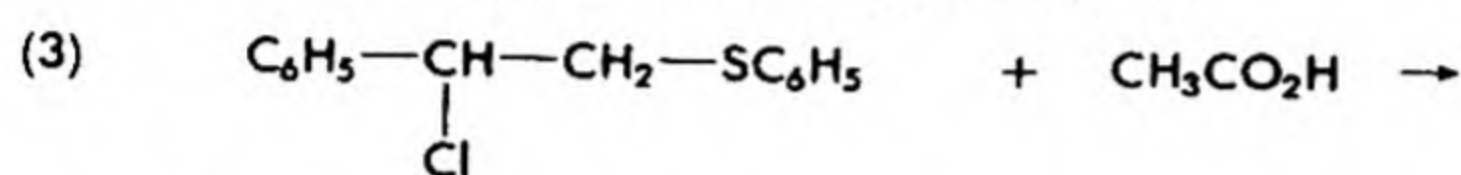
A classical proof is incomplete until both synthetic and analytical data indicate the same structure and contradictory evidence, if any, has been explained.

A cardinal principle of early structure studies is the principle of minimum change. This is based on the concept of the functional group. Since many reactions occur at and involve only the functional group, the carbon skeleton remains unchanged and new groups are found to occupy the same positions as the former groups. Thus, for example, *n*-propyl alcohol forms *n*-propyl bromide, and isopropyl alcohol forms isopropyl bromide in the usual displacement.



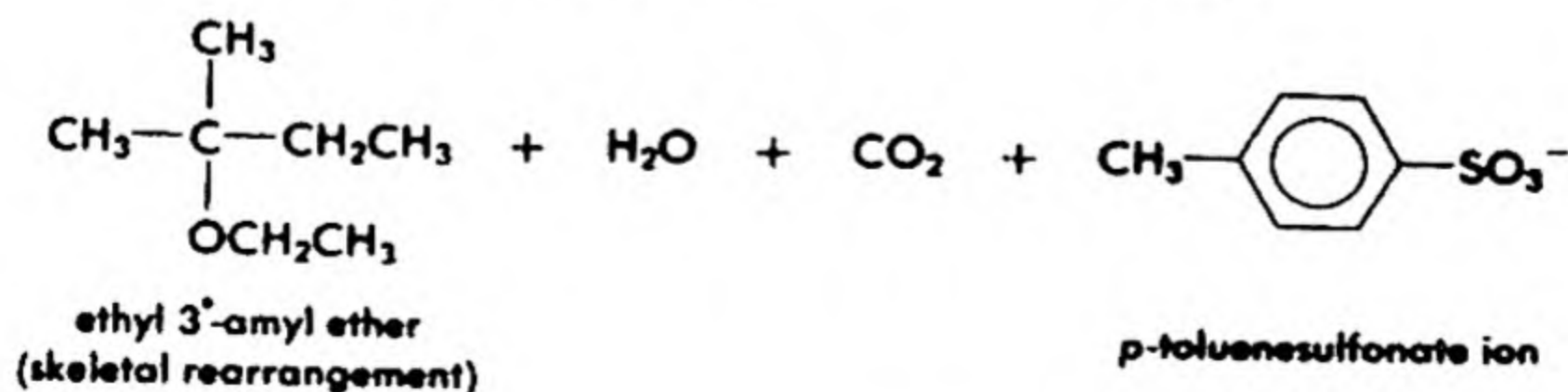
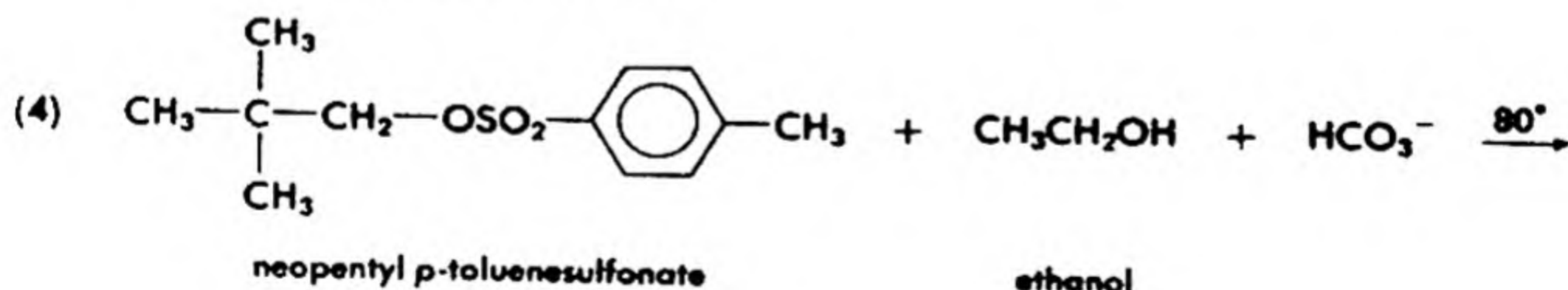
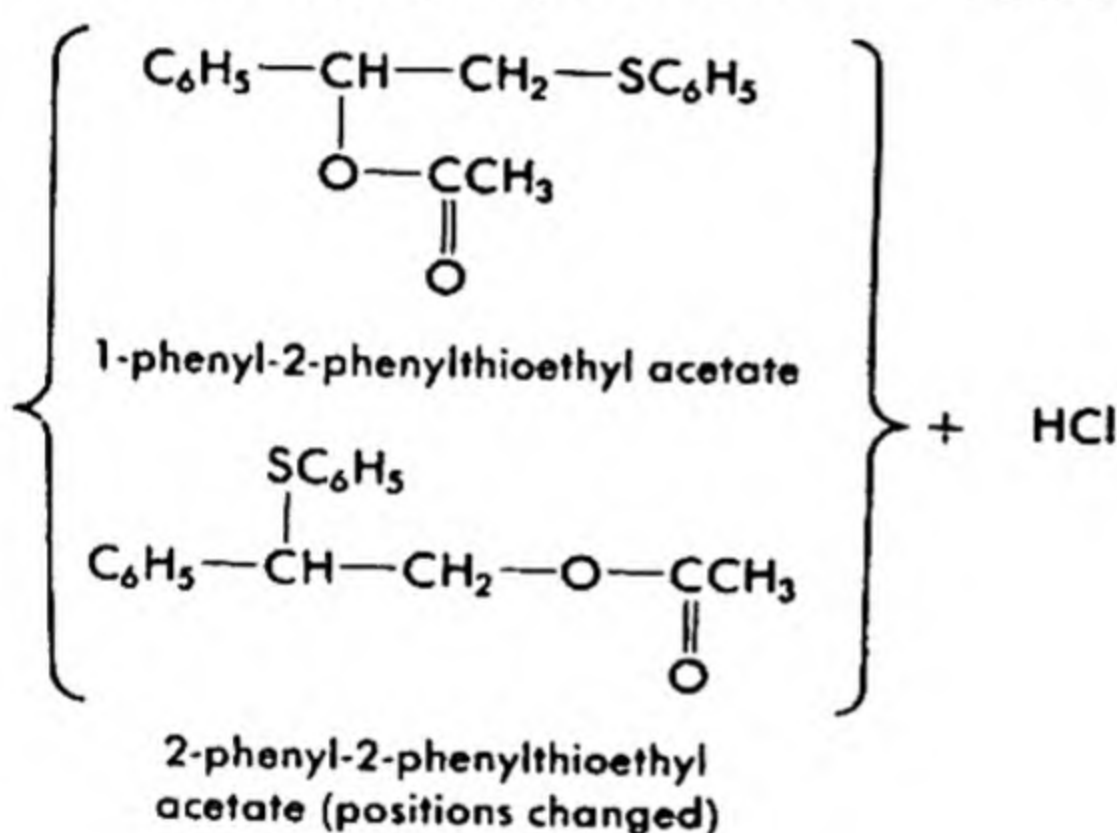
This principle allows the chemist to convert a compound of unknown structure into a related compound of known structure and thereby ascertain the nature of the carbon skeleton and the positions of the functional groups in the unknown compound.

Unfortunately, the principle of minimum change applies reliably only to a limited number of reactions, although for a much larger number it may be tentatively assumed until contrary evidence shows otherwise. Certain reactions applied to certain types of structures, notably those with displaceable groups on primary or secondary carbon atoms adjacent to chain branches, are inclined to effect rearrangements. These are reactions in which one or both of the stipulations of the principle of minimum change are violated, as in the following examples.



1-chloro-1-phenyl-2-phenylthioethane

acetic acid



Although at first rearrangements surprised and troubled organic chemists, they are now well understood, anticipated, and evincing in their own right for particular types of structures.

Those types of chemical conversions most useful to structural proof are synthesis from smaller, known units, degradation to smaller units of known or more easily determinable structure, and displacement or derivative formation to relate one structure to another known one. Many of the simplest structures can be based entirely on valence rules.

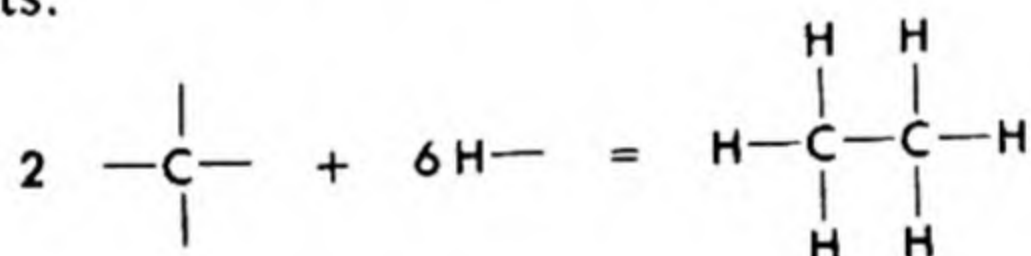
8-2 TYPICAL CLASSICAL PROBLEMS AND THEIR SOLUTIONS

In the following sections, examples are used to illustrate some of both the most fundamental and the most challenging uses of classical methods.

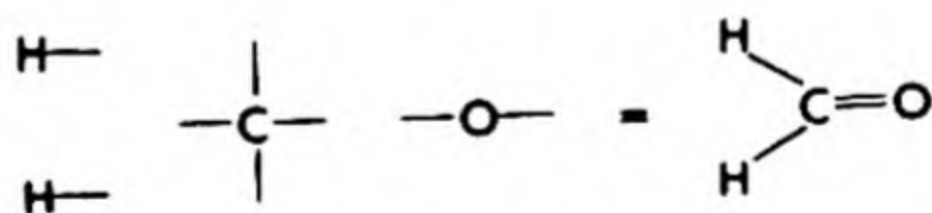
A. Unique Compounds

Those simple cases in which isomerism is impossible can be solved by application of valence rules and form the starting point for other structural proofs. Three examples may suffice to show the argument.

1. Determine the structure of C_2H_6 . This molecule consists of six univalent hydrogen atoms and two tetravalent carbon atoms. Since hydrogen can be connected only to one other atom, the carbon atoms must be connected to each other, and the hydrogens to their other available valence points.

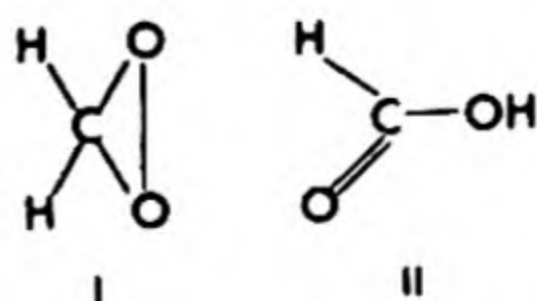


2. Determine the structure of CH_2O . Again two multivalent atoms are present, which must be connected together. However, insufficient hydrogen atoms are present to satisfy all of the remaining valence points of carbon and oxygen. Therefore, these two atoms must satisfy each other by additional bonds.



Sometimes slight additional evidence can be used to establish an ambiguous case.

3. Determine the structure of CH_2O_2 , formic acid. By the above principles, two are possible.

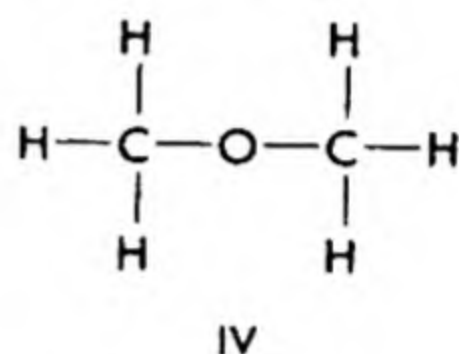
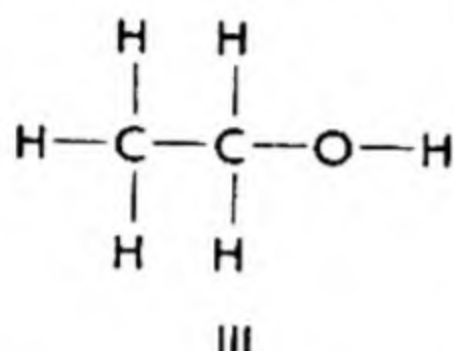


Structure I does not explain the acidic properties of formic acid, since hydrogen on carbon is not usually acidic (§7-1B). Structure II is better in

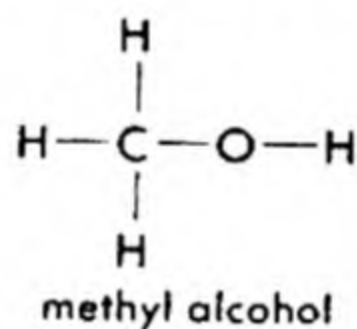
this regard, since hydrogen on oxygen often shows acidic properties. Furthermore, I has a peroxide group (—O—O—), which has strong oxidizing properties in those compounds known to contain it (e.g., H—O—O—H , Na_2O_2). Formic acid has no tendency to be an oxidizing agent. Here again, formula II is better and is chosen as the correct formula for formic acid.

B. Structure by Analogy

The principle of homology is very useful for structural analysis. The cases of isomeric ethyl alcohol and methyl ether, both $\text{C}_2\text{H}_6\text{O}$, are easily disposed in this way. The two structures are III and IV.



One of these is a homolog of methyl alcohol, a unique structure for



CH_4O . A comparison of the weakly acidic properties (e.g., evolution of hydrogen when treated with sodium metal) and relatively high boiling points of ethyl alcohol and methyl alcohol suggests III rather than IV for ethanol, since the same group with possible acidic hydrogen, OH , occurs in both. The ether, both more volatile and nonacidic, fits IV better.

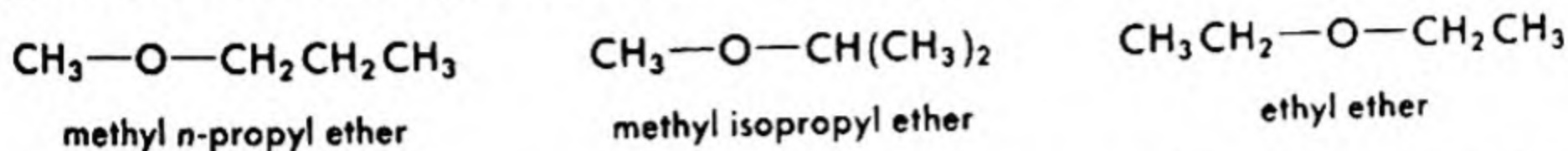
To corroborate argument by analogy, independent chemical conversions may sometimes be used. When acetic acid, $\text{C}_2\text{H}_4\text{O}_2$, is chlorinated, a monochloro, dichloro, and trichloro derivative, respectively, $\text{C}_2\text{H}_3\text{O}_2\text{Cl}$, $\text{C}_2\text{H}_2\text{O}_2\text{Cl}_2$, and $\text{C}_2\text{HO}_2\text{Cl}_3$, can be formed, all with acidic properties; the fourth hydrogen cannot be replaced by the most drastic or prolonged treatment with chlorine. However, thionyl chloride converts acetic acid to acetyl chloride, $\text{C}_2\text{H}_3\text{OCl}$, with entirely different properties, and with one hydrogen and one oxygen together replaced by chlorine. The student should be able to show how this supplements the homology to formic acid in proving the accepted structure for acetic acid.

C. Structures of Ethers and Esters by Cleavage and Synthesis

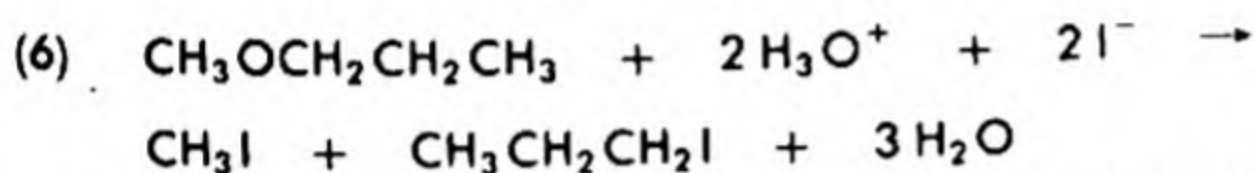
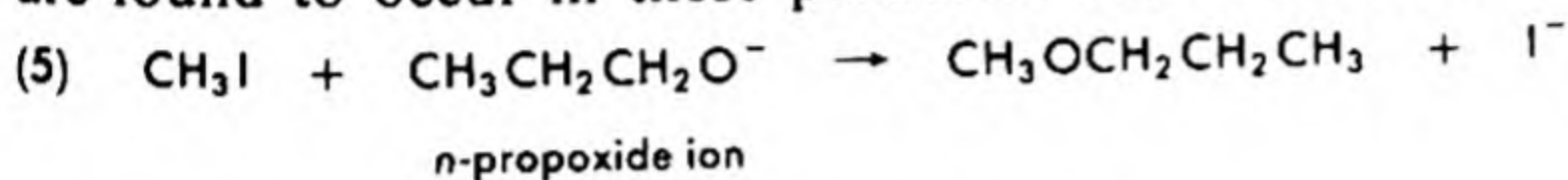
The simple examples given below may seem so obvious as to appear trivial, but the method illustrated in them has been very important to the

establishment of ether or ester groups in complex compounds such as the alkaloid codeine, the vitamin biotin, and the flavoring essence eugenol.

Three ethers with the formula $C_4H_{10}O$ exist (the isomeric alcohols having been eliminated by homologic reasoning). They are listed below.

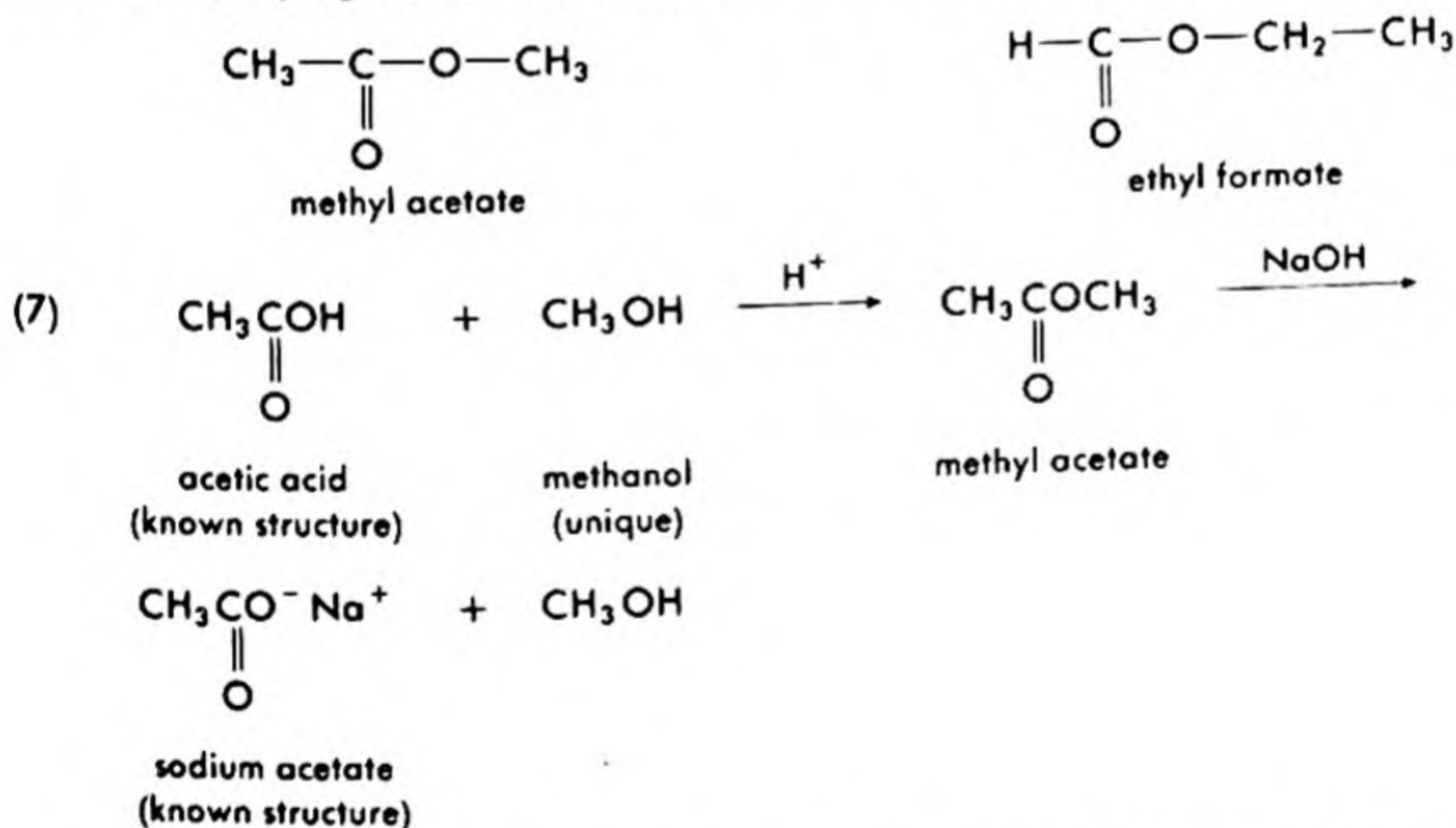


That compound prepared from sodium *n*-propoxide (structure independently determined) and methyl iodide (unique) and which gives methyl iodide and *n*-propyl iodide upon cleavage with hydriodic acid would obviously seem to be methyl *n*-propyl ether, and, since no rearrangements are found to occur in these particular reactions, the obvious is, in this



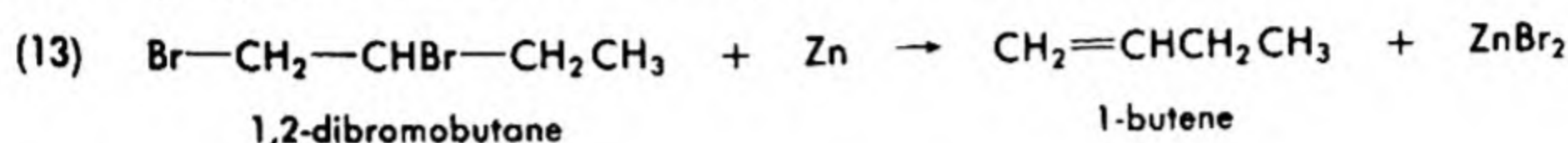
case, vindicated. Analogous data establish the remaining structures for their respective compounds.

For esters, once the structure of the ester function is established, similar synthesis and cleavage methods serve to prove overall structures, as for the two $C_3H_6O_2$ isomers (outline 7 and its complement).



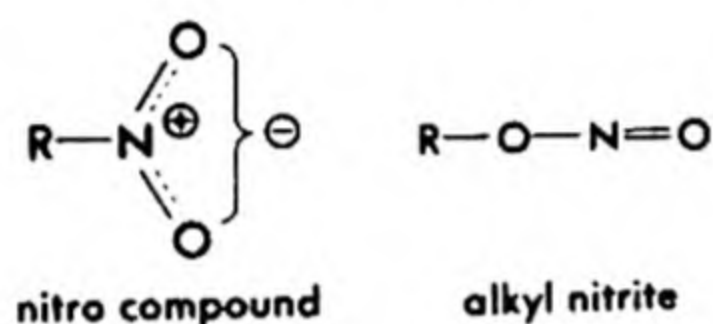
The independent structure determination of the *n*-propoxide and isopropoxide ions was required in one of the above examples and the related iodides implied in the same example. These can be related to the corresponding alcohols, which are established by oxidation and reduction reactions. One of the alcohols forms a carboxylic acid, $C_3H_6O_2$, by treatment with a dichromate in acid; the other forms a ketone, C_3H_6O (since it

Perhaps it should be pointed out that ordinary addition reactions can give no direct evidence for the position of the double bond. For example, the different dibromides, isomers of $C_4H_8Br_2$, obtained from 1-butene and 2-butene are indistinguishable structurally without further extensive investigation; indeed, the best way to prove the structures of these dibromobutanes is to establish the structures of the butenes from which they can be prepared and to which they revert on treatment with zinc.

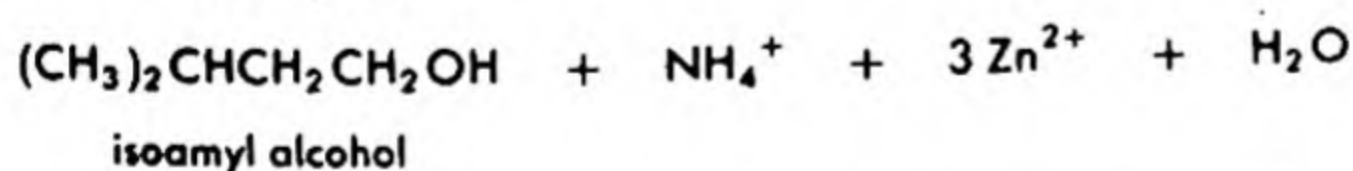
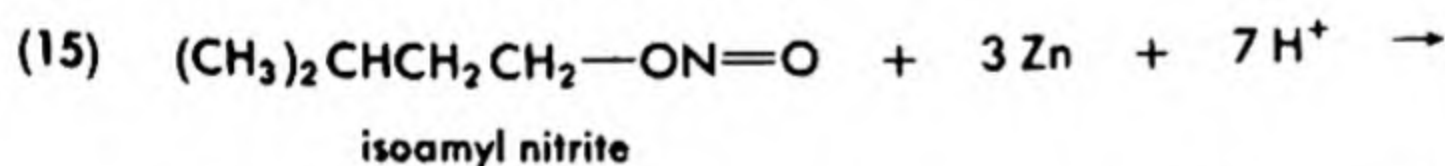
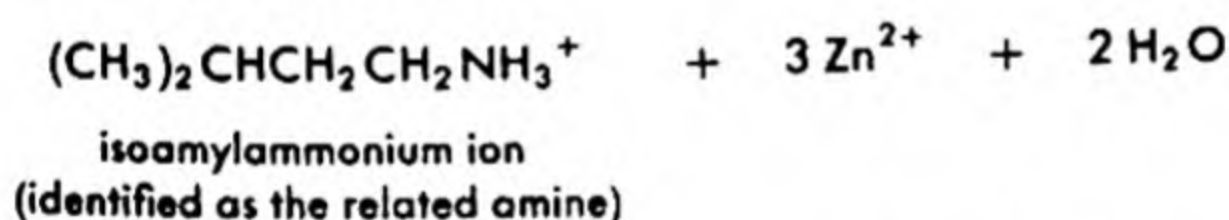
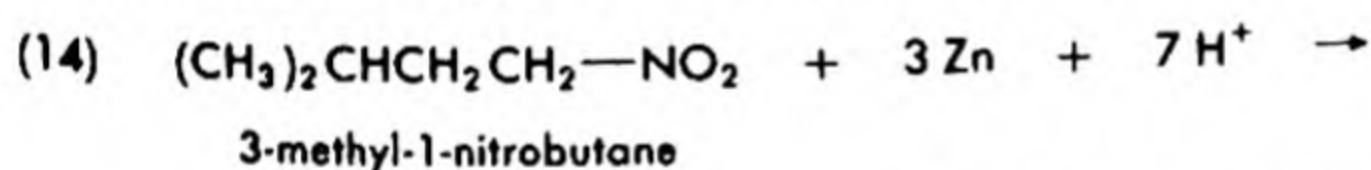


E. Functional Isomers

Certain isomers differ in the position of attachment of atoms within the functional group to a hydrocarbon group, as in the case of nitro compounds and nitrites.

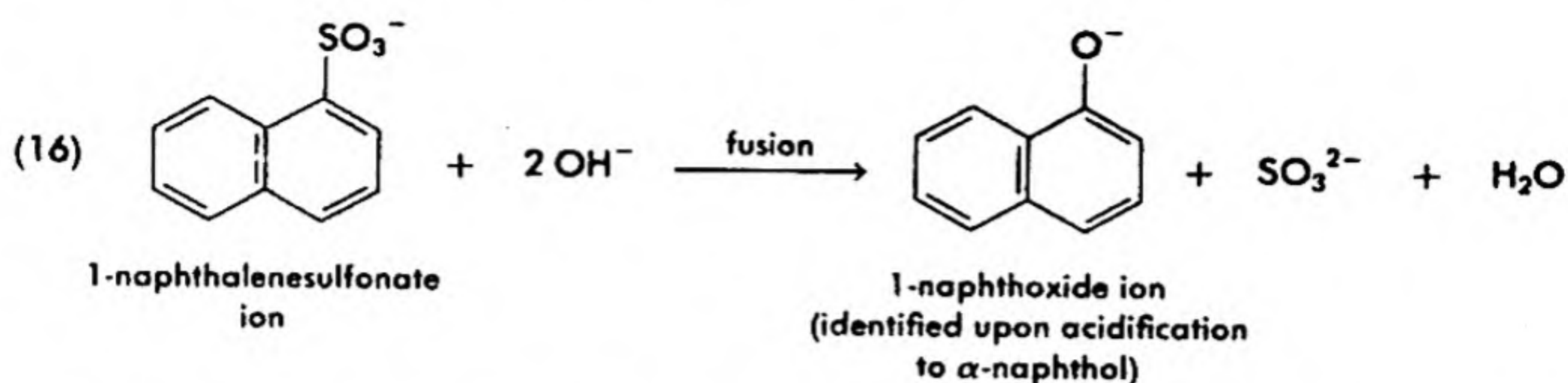


It is usually a simple matter to establish the point of attachment by a reaction which cleaves off all of the group but the atom attached to carbon. In this case, reduction is effective.

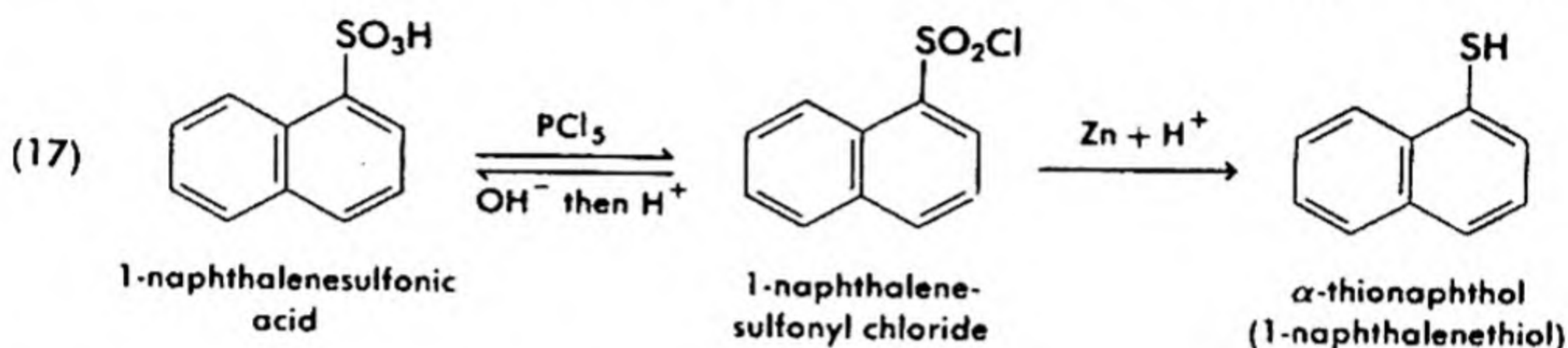


Since the nitrogen atom from the nitro group remained, and the oxygens were removed, the attachment of the nitro group by nitrogen in the original compound is suggested (but not conclusively proved without corroboration). A similar argument suggests attachment of the nitrite group by oxygen to the carbon.

The danger of oversimplification without corroborative evidence is indicated by the result of fusion of an arenesulfonate with sodium hydroxide, which suggests presence of an oxygen atom between sulfur and carbon.

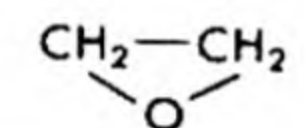


Contrary evidence from reduction of a sulfonic acid derivative indicates that the sulfur atom, not oxygen, is attached to the ring, outline (17).

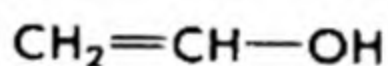


F. Structural Ambiguity: Tautomerism

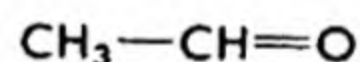
Of the three possible structures corresponding to C_2H_4O , one can be established as belonging to the gas ethylene oxide. The problem is to assign a structure to acetaldehyde, V or VI.



ethylene oxide

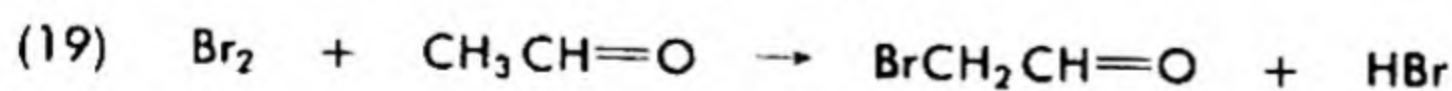
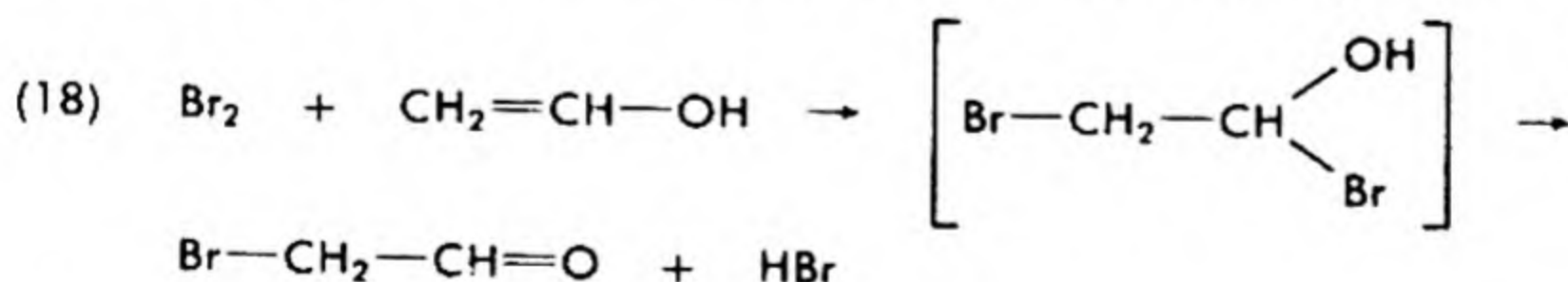


V



VI

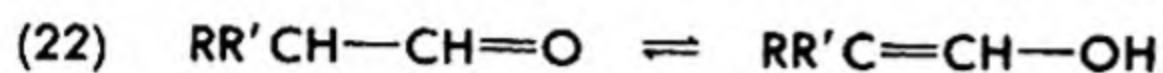
One would expect V to evolve hydrogen by reaction with sodium and to *add* bromine rapidly. Acetaldehyde is reduced by sodium, but gives little hydrogen. It is rapidly *substituted* by bromine when acid is present. This may not be inconsistent with V, since the dibromo adduct may well be unstable (eq. 18). Substitution would also be expected of VI.



Controlled oxidation of ethanol gives acetaldehyde. This logically would indicate VI, as the more acidic hydrogen on oxygen would be expected to participate, rather than that on the methyl group.

Evidence from synthesis is contradictory. Addition of water to acetylene, hydrolysis of vinyl chloride, and cleavage of vinyl ether all would be expected to give V (outline 20); acetaldehyde is the product in each case.

The uptake is related to the amount of enol present, which appears to be less than 1%. This and other related data, including the close similarity in reactions of all aldehydes, lead us to choose the formula VI to represent acetaldehyde, but with the fact in mind that the enol (e.g., vinyl alcohol) structure is necessary to explain a few of the properties of aldehydes of the type $RR'CH-CH=O$. The equilibrium between tautomers is represented by eq. (22). Ketones with α -hydrogen are also tautomeric.



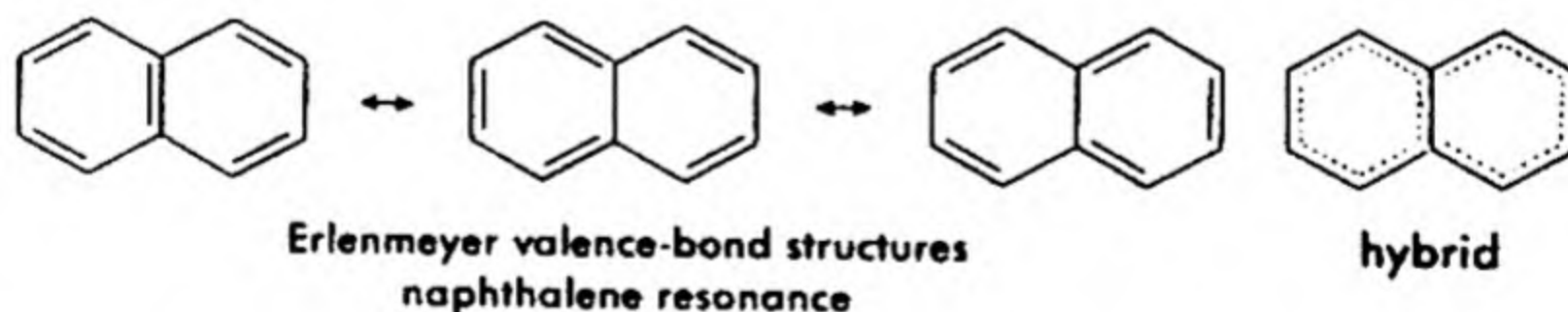
G. Mesomeric Structure: Resonance and the Benzene Problem

The newly formed structure theory of Kekulé (1857) received its severest test almost immediately with the case of benzene. Although this was resolved (1872) as a supposed equilibrium, it was not until quantum theory and the concept of resonance had been applied that all of the properties of benzene were explained in terms of its structure (§7-3A(1)).

At the time Kekulé first proposed a structure for benzene (1865), it was by no means clear that the structure involved a six-membered ring. Different chemists proposed a variety of structures (Fig. 7-4); some of them attempted to apply vague and questionable valence concepts to explain the peculiar properties of the benzene ring.

The structure of benzene remained a problem until X-ray diffraction studies and ultraviolet spectral interpretations showed conclusively that the carbon skeleton of benzene is, indeed, a regular hexagon, that all six C—H bonds are identical, and that all six C—C bonds are identical. Benzene can be said to have a nonclassical structure,¹ since classical structural methods proved inadequate to define its structure, and classical valence theory was incapable of describing its structure.

Other aromatic compounds show similar mesomerism; naphthalene has three Erlenmeyer structures that correspond to the Kekulé structures of benzene, but none of the three is real, as the molecule is, like benzene, a resonance hybrid.



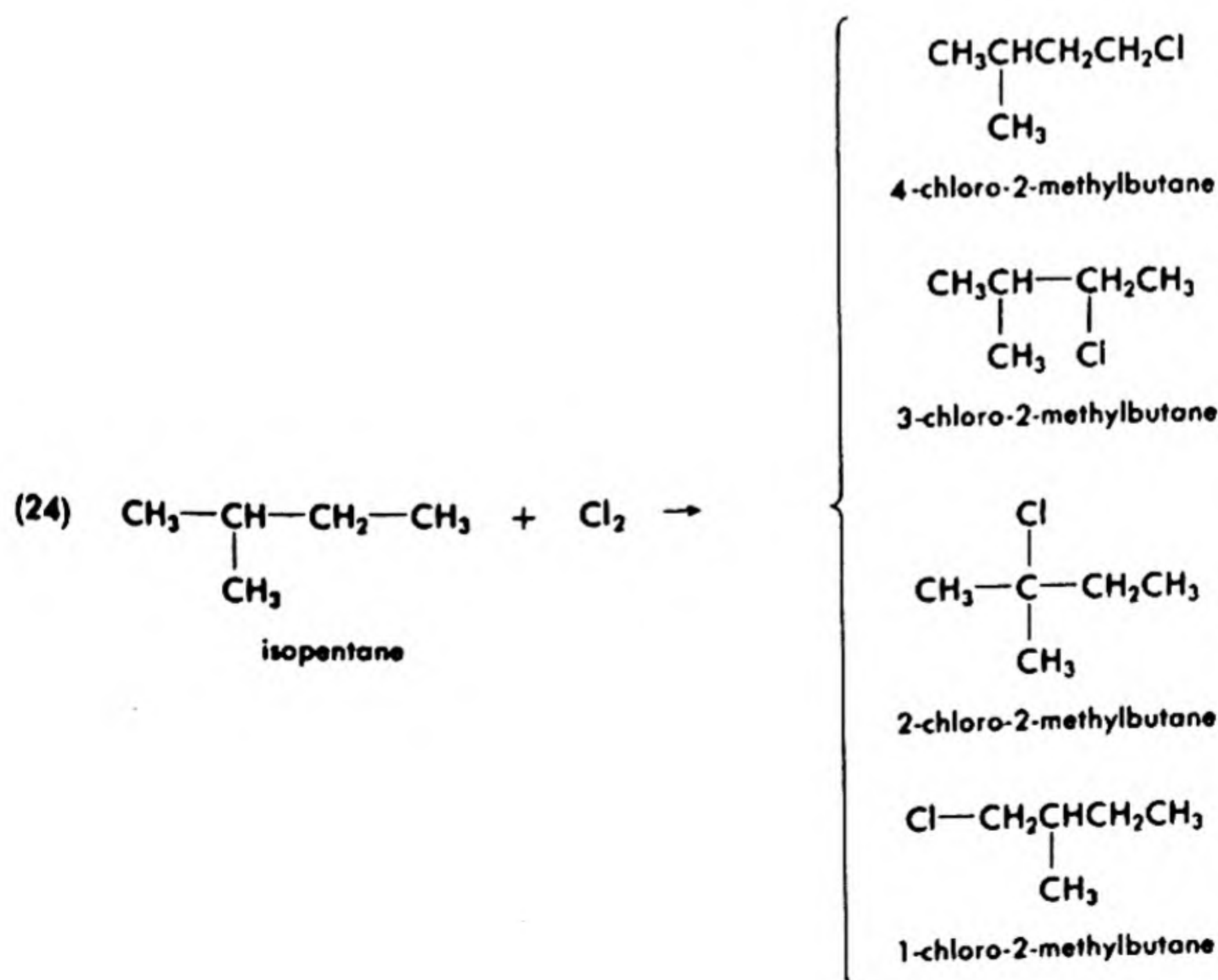
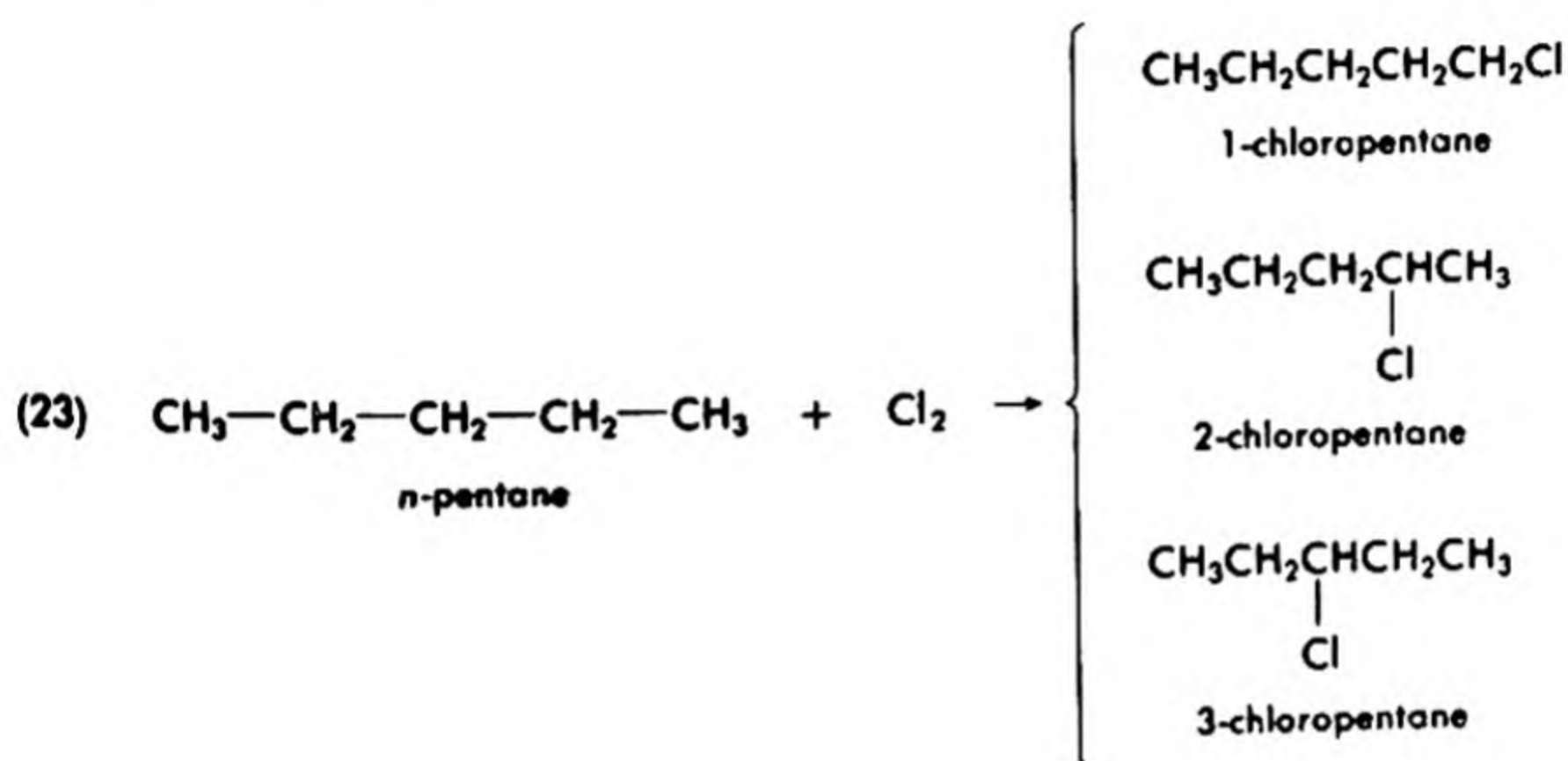
H. Isomer Number Methods

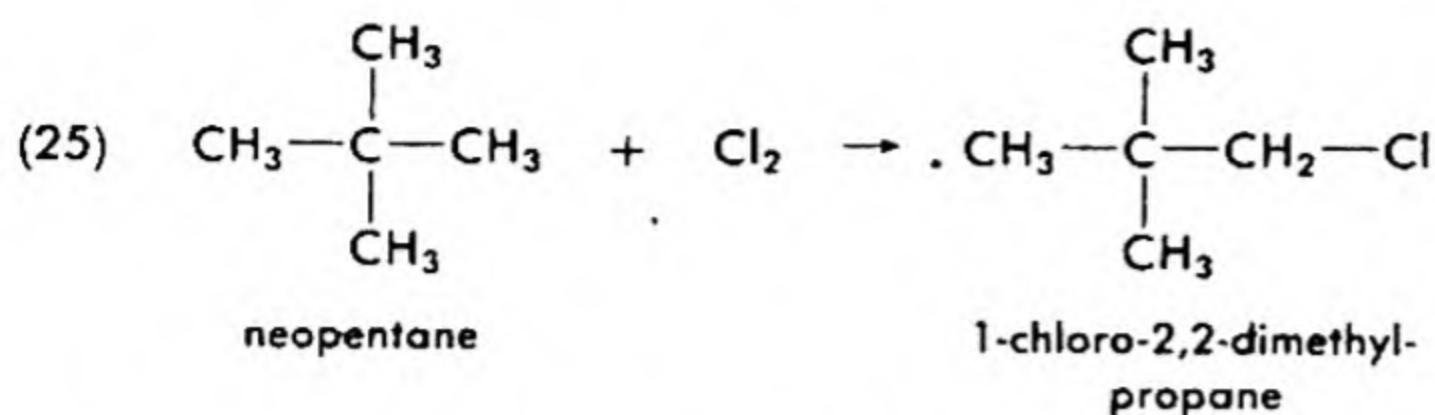
Data regarding the number of isomers produced by substitution in a compound, or regarding the numbers of isomers that form a compound

¹ What is considered nonclassical depends on the historical viewpoint. Chemists now talk about nonclassical aromatic systems. Each generation of chemists considers as "nonclassical" its own harvest of unexpected, pattern-shattering phenomena.

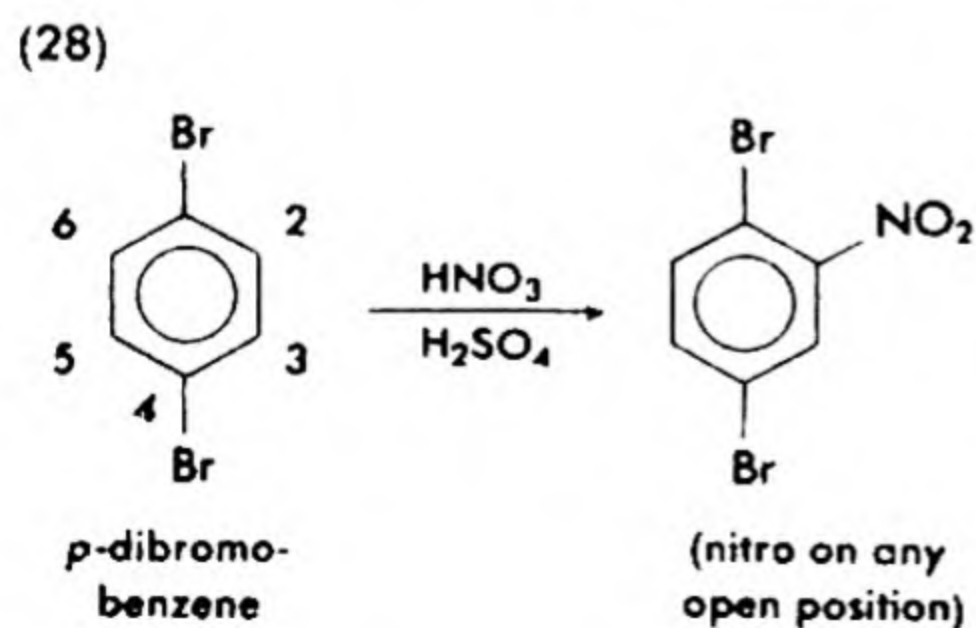
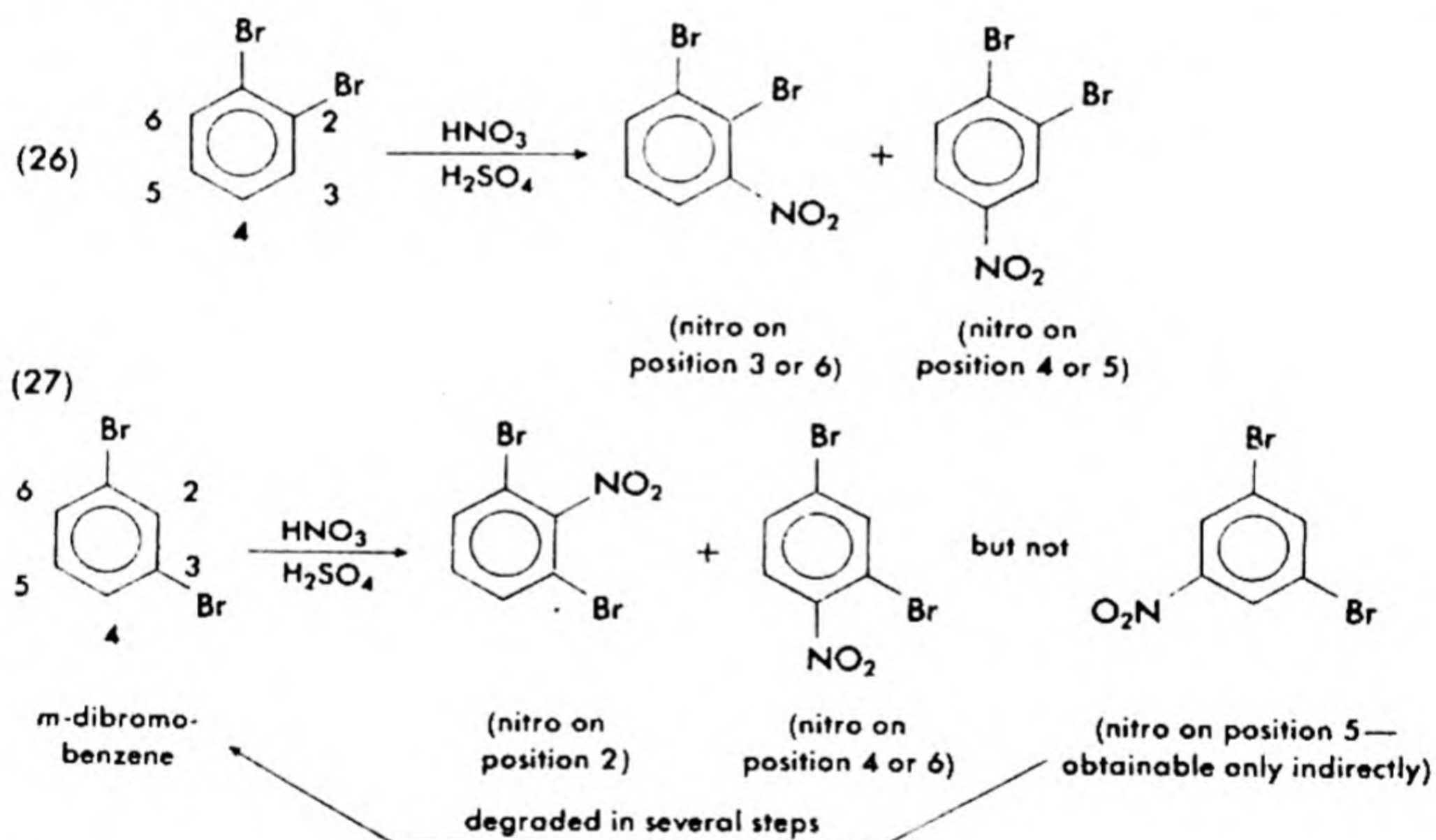
by removal of substituent groups, can sometimes be useful for discrimination between structures.

The pentane which boils at 9.5° gives a single monochloro derivative, $C_5H_{11}Cl$. That which boils at 27.9° gives four monochloro derivatives. That which boils at 36.1° yields three monochloro derivatives. From the outlines below the structure of each of the isomeric compounds with specified properties should be apparent. The products were originally isolated by careful distillation, but now vapor phase chromatography provides a more sensitive method of separation.

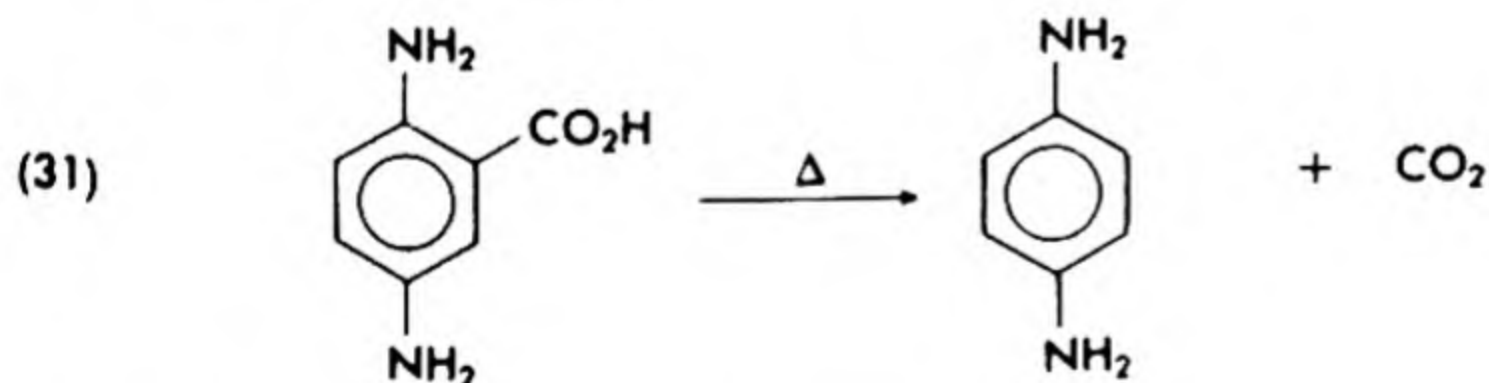
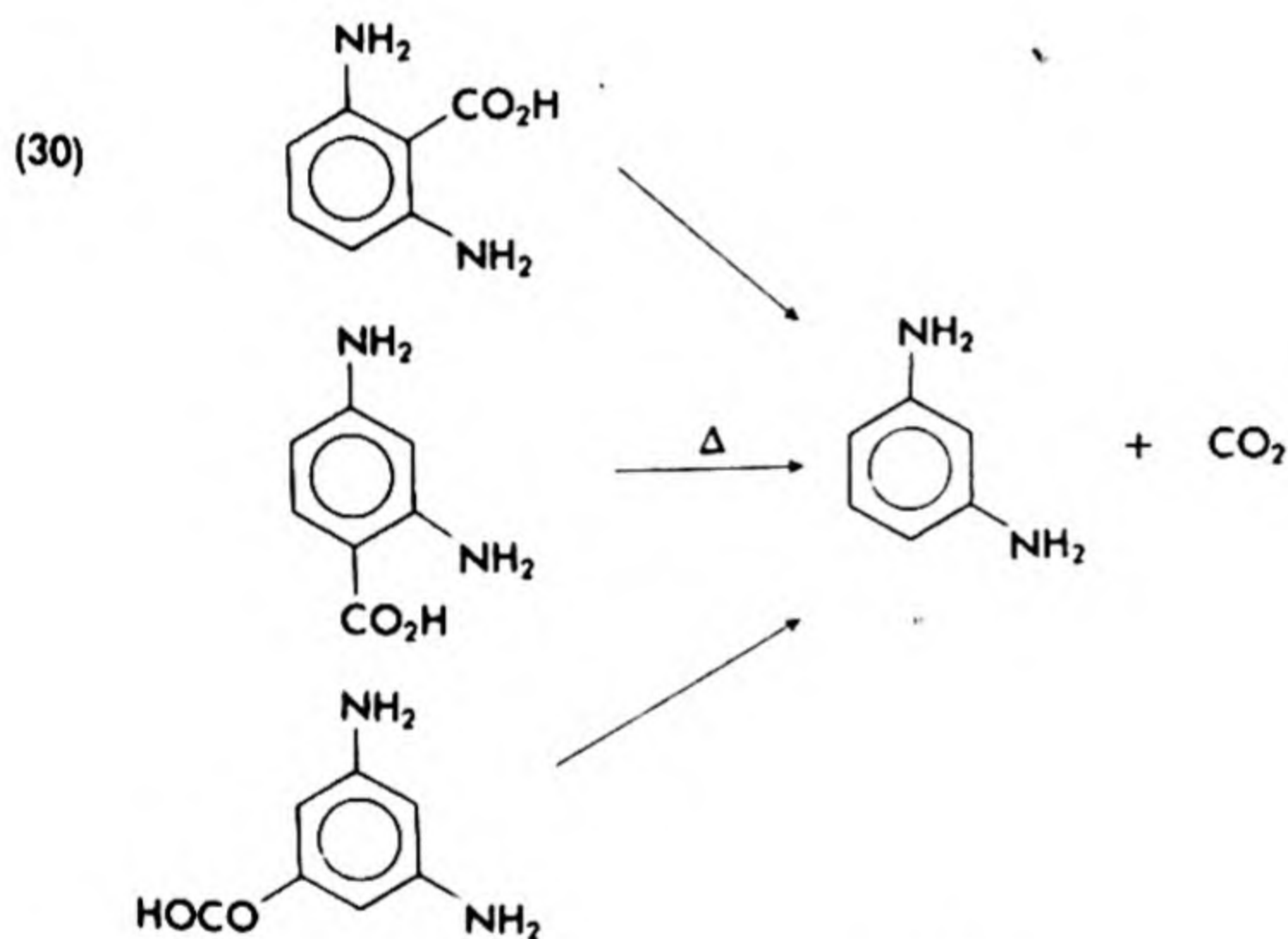
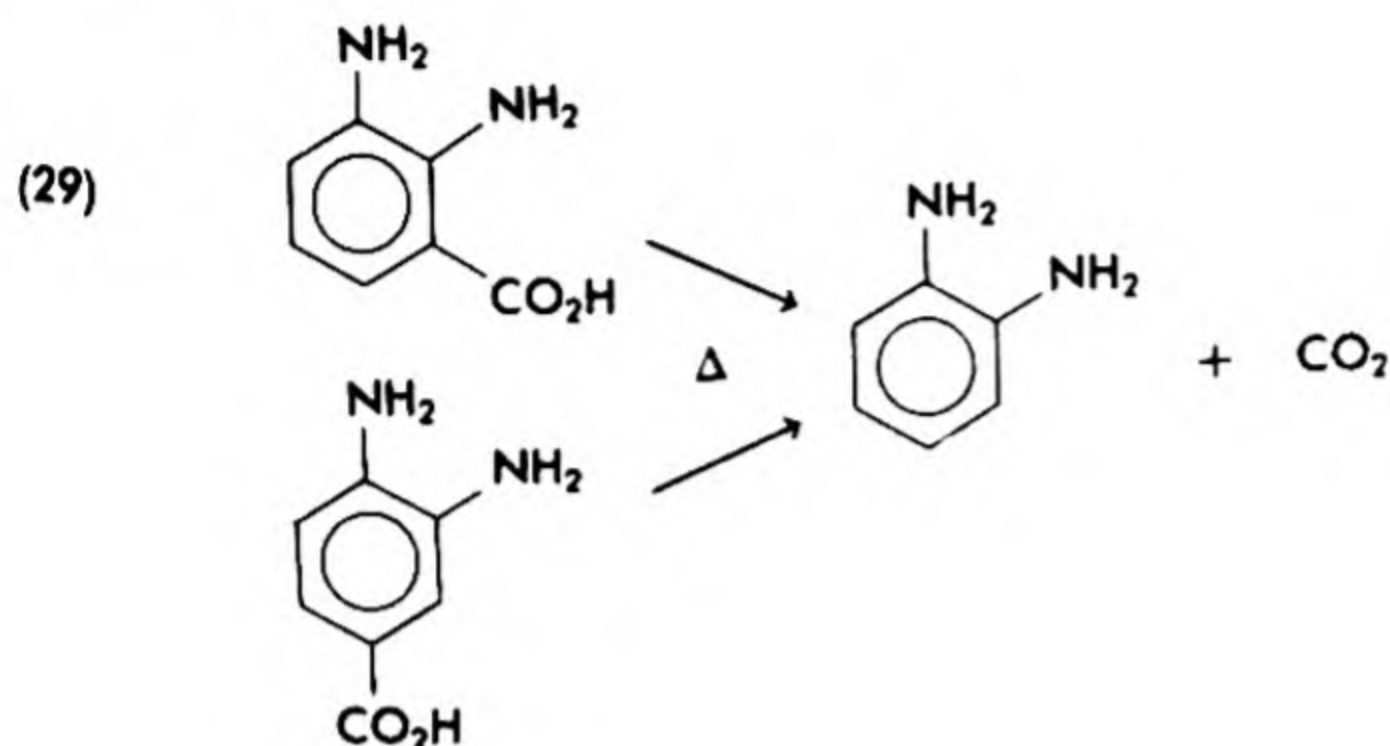




The isomer number method, called the Körner-Griess-Salkowsky method from its early users, or the *absolute method*, has been widely applied to the problem of positional isomerism in benzene derivatives. In principle, disubstituted benzene derivatives give different numbers of products upon introduction of one more substituent group. In actual fact, fewer products are often formed in amounts great enough to be isolated than theoretically would be anticipated, due to internal influences which assure that most of the substitution will occur at favored positions. Thus, the results of substitution studies must be interpreted with caution (see outlines 26–28).

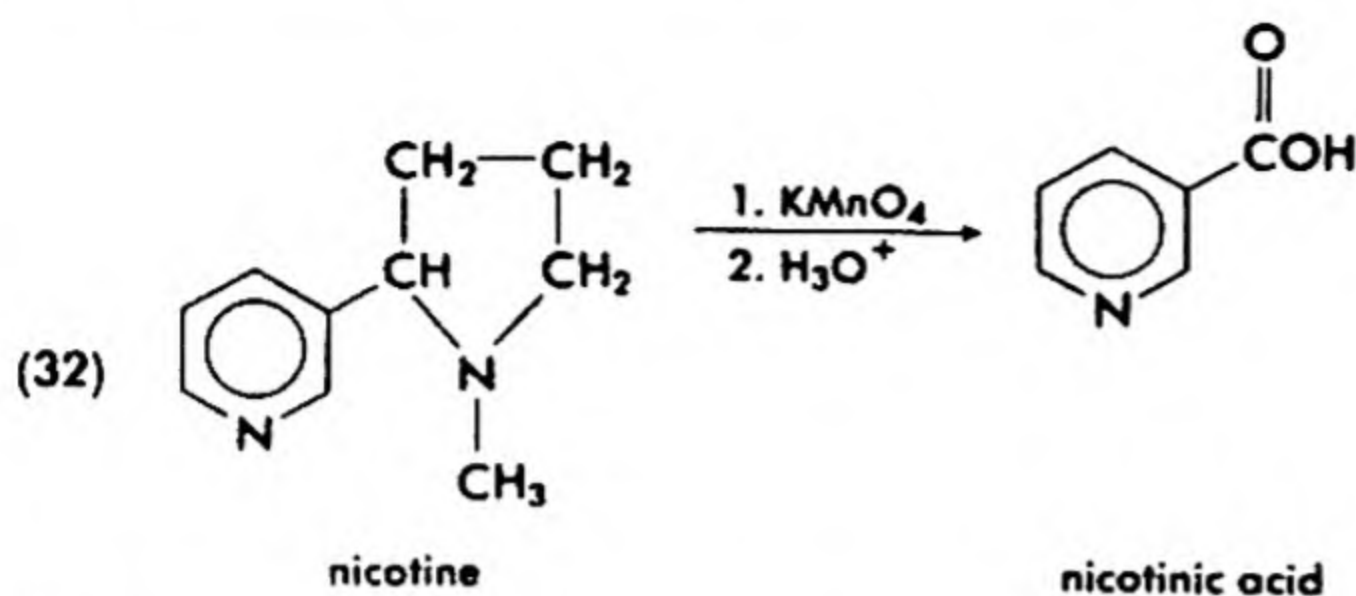


Removal of a group from all known isomers of a compound is more reliable, provided that the theoretical number of isomers is known (outlines 29–31).

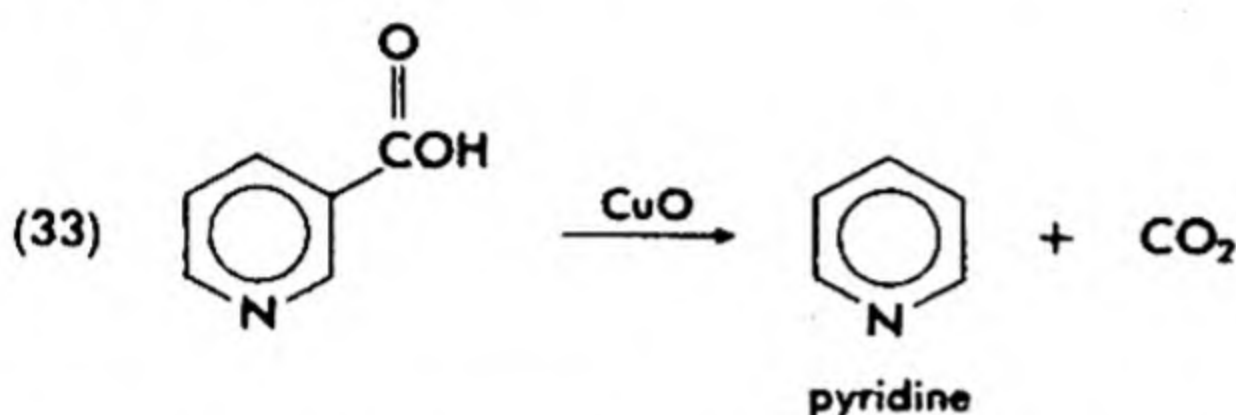


I. Degradation in Complex Structures

The importance of degradation to structural analysis can be illustrated in a part of the evidence used to establish the structure of nicotine, the main alkaloid in tobacco. Oxidation of nicotine with alkaline permanganate and neutralization of the product gives nicotinic acid (which is of interest in its own right, as it is a B vitamin).



The nicotinic acid can be further degraded, by heating with cupric oxide, to pyridine.



These degradations establish that nicotine and nicotinic acid are substituted pyridines. Other reactions may be used to establish the position of the carboxyl group in nicotinic acid (and thus the remainder of the molecule in nicotine) and to elucidate the nature of the $C_5H_{10}N$ group in nicotine.

QUESTIONS AND PROBLEMS

1. Does structural analysis by isomer number constitute proof of structure? Explain.
2. Show whether the butanes can be distinguished structurally by their monohalogen derivatives. Explain, with formulas.
3. The five hexanes have the following properties.

	Boiling Point, °C	Number of Monohalogen Derivatives
I	49.7	3
II	58.1	2
III	60.3	5
IV	63.3	4
V	69.0	3

- a. Write the equation for the chlorination of hexane, using molecular formulas.
- b. Write structural formulas for all of the hexanes.
- c. Write structural formulas for all of the monochloro derivatives of each hexane. Check that there are no duplications by giving their IUPAC names.
- d. Write out the structures which cannot be distinguished by the number of their monochloro derivatives.
- e. Write the structure for II, III, and IV.

4. Show how ozone can be used to differentiate structurally between 2-hexene and 3-hexene. How suitable would an ordinary addition reaction, such as bromination, be for this purpose? (Think in terms of what one may readily observe in the laboratory, not paper differences.)

5. Explain why it was difficult to assign a structure to benzene in agreement with its properties.

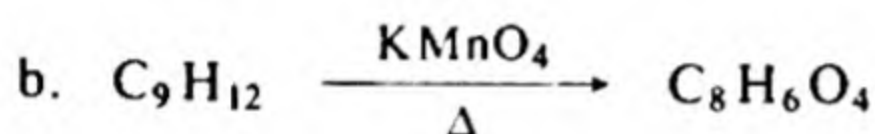
6. If valence-bond structures have no reality in a resonance-delocalized system, why are they used? What is a resonance hybrid? By comparing acetic acid and acetate ion, explain why formulation of a resonance hybrid proves to be difficult.

7. Why is it objectionable on theoretical grounds to formulate acetic acid with a valence-bond structure, but not as objectionable so to formulate acetaldehyde?

8. Determine the structural formulas of the benzene derivatives that give the following data. Write the common and IUPAC names of the hydrocarbons.

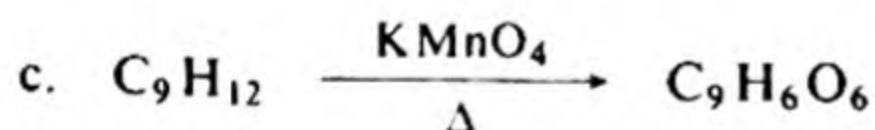


The same $\text{C}_8\text{H}_{10} + \text{Br}_2 \xrightarrow{\text{Fe}}$ mixture of two isomers, $\text{C}_8\text{H}_9\text{Br}$

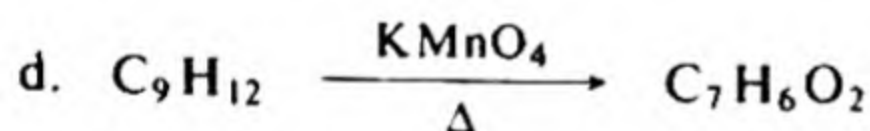


The same $\text{C}_9\text{H}_{12} + \text{Br}_2 \xrightarrow{\text{Fe}}$ mixture of four isomers, $\text{C}_9\text{H}_{11}\text{Br}$

The $\text{C}_8\text{H}_6\text{O}_4 + \text{Br}_2 \xrightarrow{\text{Fe}}$ mixture of two isomers, $\text{C}_8\text{H}_5\text{O}_4\text{Br}$

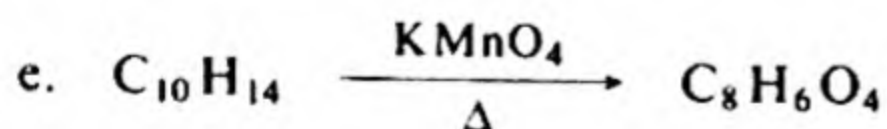


The same $\text{C}_9\text{H}_{12} + \text{Br}_2 \longrightarrow$ a single product, $\text{C}_9\text{H}_{11}\text{Br}$



The same $\text{C}_9\text{H}_{12} + \text{Br}_2 \xrightarrow{\text{Fe}}$ mixture of three isomers, $\text{C}_9\text{H}_{11}\text{Br}$

The same $\text{C}_9\text{H}_{12} + \text{Cl}_2 \xrightarrow{\text{light}}$ mixture of two isomers, $\text{C}_9\text{H}_{11}\text{Cl}$



The same $\text{C}_{10}\text{H}_{14} + \text{Br}_2 \xrightarrow{\text{Fe}}$ mixture of three isomers, $\text{C}_{10}\text{H}_{13}\text{Br}$

The $\text{C}_8\text{H}_6\text{O}_4 + \text{Br}_2 \xrightarrow{\text{Fe}}$ mixture of three isomers, $\text{C}_8\text{H}_5\text{O}_4\text{Br}$

9. Give analytical and synthetic evidence to show that toluene has the structure of methylbenzene.

10. Why are only two compounds with the molecular formula $\text{C}_2\text{H}_4\text{O}$ capable of isolation?

11. Show how the structures of the following ethers can be established by cleavages and by synthesis from alcohols, phenols, and halides.

a. the three $C_4H_{10}O$ isomers b. the two $C_6H_5(C_2H_5O)$ isomers

12. Write the structural formulas for and name the ethers identified by the following data. Use a handbook to look up the physical properties.

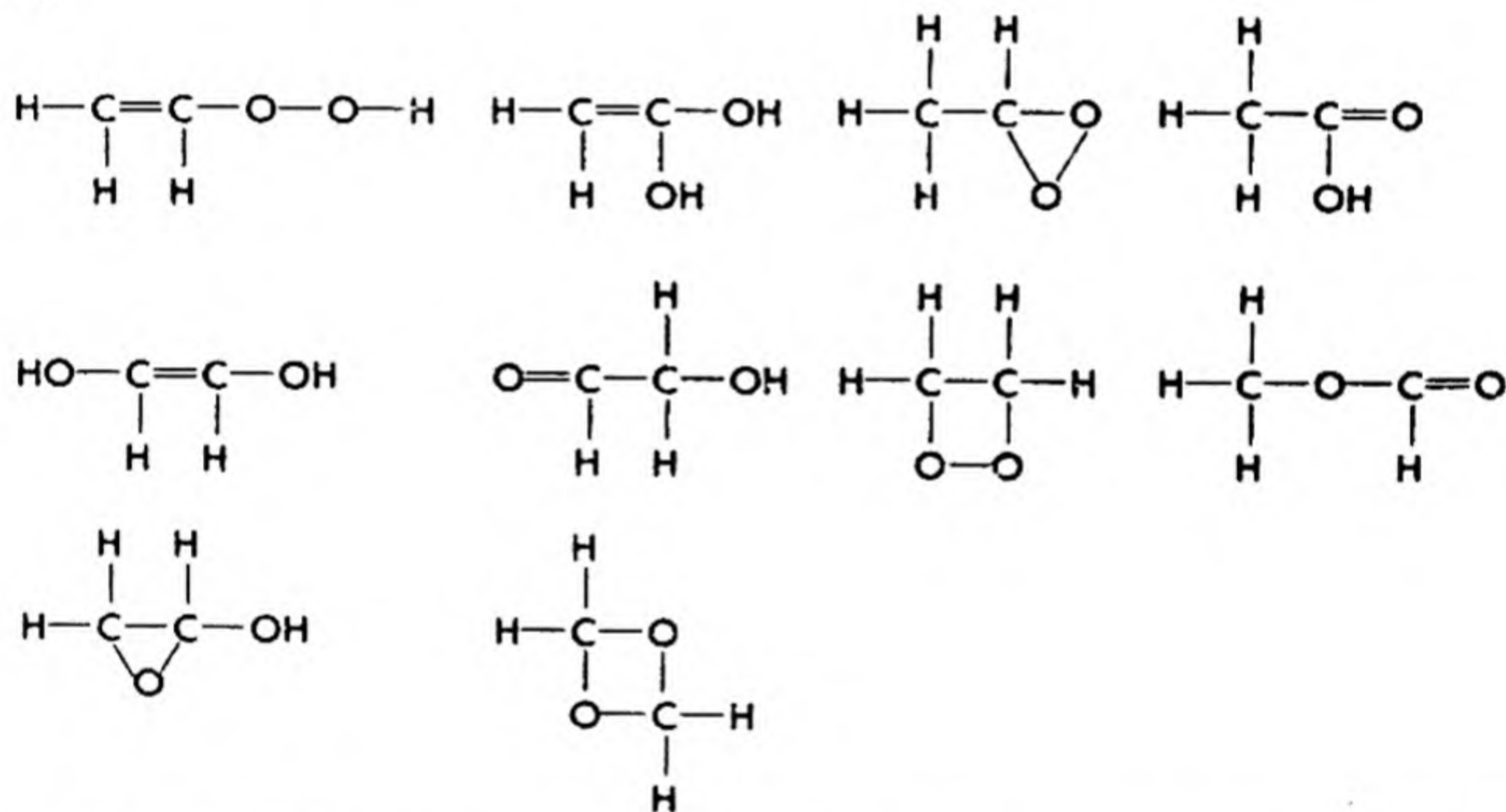
a. Ether, b.p. $33-35^\circ$, on treatment with HI gives a single iodide, b.p. $71-72^\circ$.

b. Ether, b.p. $59-60^\circ$, on treatment with HI gives products collected at $41-44^\circ$ and $119-121^\circ$ by distillation.

c. Ether, b.p. $150-154^\circ$, on treatment with HI gives a volatile compound, b.p. $42-43^\circ$, and a compound containing no halogen, b.p. $175-181^\circ$.

d. Ether, b.p. $203-208^\circ$, insoluble in dilute sodium hydroxide solution, on treatment with HI gives a volatile compound, b.p. $43-44^\circ$, and a water-soluble compound which, on evaporation, forms crystals, m.p. $101-103^\circ$. Recrystallization of the solid from water gave a purified material, m.p. $103-104^\circ$.

13. Which of the structures below would be unlikely to be isolated as such? Why?



14. Which of the structures in Question 13 would be expected, if they could be isolated, to be notably acidic? Why?

15. Write equations for reactions which show that the oxygen atom connecting the acyl groups in an anhydride is attached to both carbonyl groups, not to some other part of the molecule.

16. Interpret the data given in §8-2B concerning reactions of acetic acid. Write equations.

17. Write equations for the reactions mentioned in §8-2C as evidence for structures of *n*-propyl and isopropyl alcohols. Show how these reactions establish the respective structures.

18. Show how the structures of methyl isocyanide, $CH_3-N\equiv C$, and acetonitrile, $CH_3-C\equiv N$, can be differentiated. A mixture of both is obtained by reaction of methyl iodide with silver cyanide.



Structure and Physical Properties

9-1 SIMPLY DETERMINED PROPERTIES

Such properties as melting points, boiling points, specific gravities, and solubility relationships can be determined with "common" apparatus such as thermometers, ordinary glassware, and a chemical balance. Add a refractometer and one can readily obtain a truly constitutive property, the refractive index, with remarkable ease from a drop or so of sample.

Although there are rough relationships between chemical structure and the first four mentioned properties, perhaps sufficient to justify their brief discussion, the relationships are so crude as to have little value for the determination of structure. The common properties do give some information regarding the gross molecular nature of compounds as well as means of identification, estimation of purity, and separation of substances.

A. Boiling Points and Melting Points

Nonpolar compounds such as the alkanes, and slightly polar compounds without hydrogen bonding possibilities, such as alkyl halides, ethers, and tertiary amines, follow essentially the boiling point relationship to molecular weight shown in Fig. 9-1A. Such a curve indicates relatively low attractive forces between molecules of the compound. The bromides and iodides are even lower boiling than the alkanes of the same molecular weight because of the high masses of the bromine and iodine atoms (Fig. 9-1B). The smaller the number of atoms in a molecule of a given molecular weight, the larger is the proportion of its internal energy that goes into molecular velocity.

Hydrogen bonding greatly increases the attractive forces between molecules, hence requires higher energy content, thus higher temperatures for boiling to occur. Since boiling is a process of separation of molecules from the close but random packing of the liquid to the widely spaced, freely moving gas state (at atmospheric pressure), work must be done against the attractive forces to bring about boiling. This work influences mainly the heat of vaporization, but indirectly influences the boiling

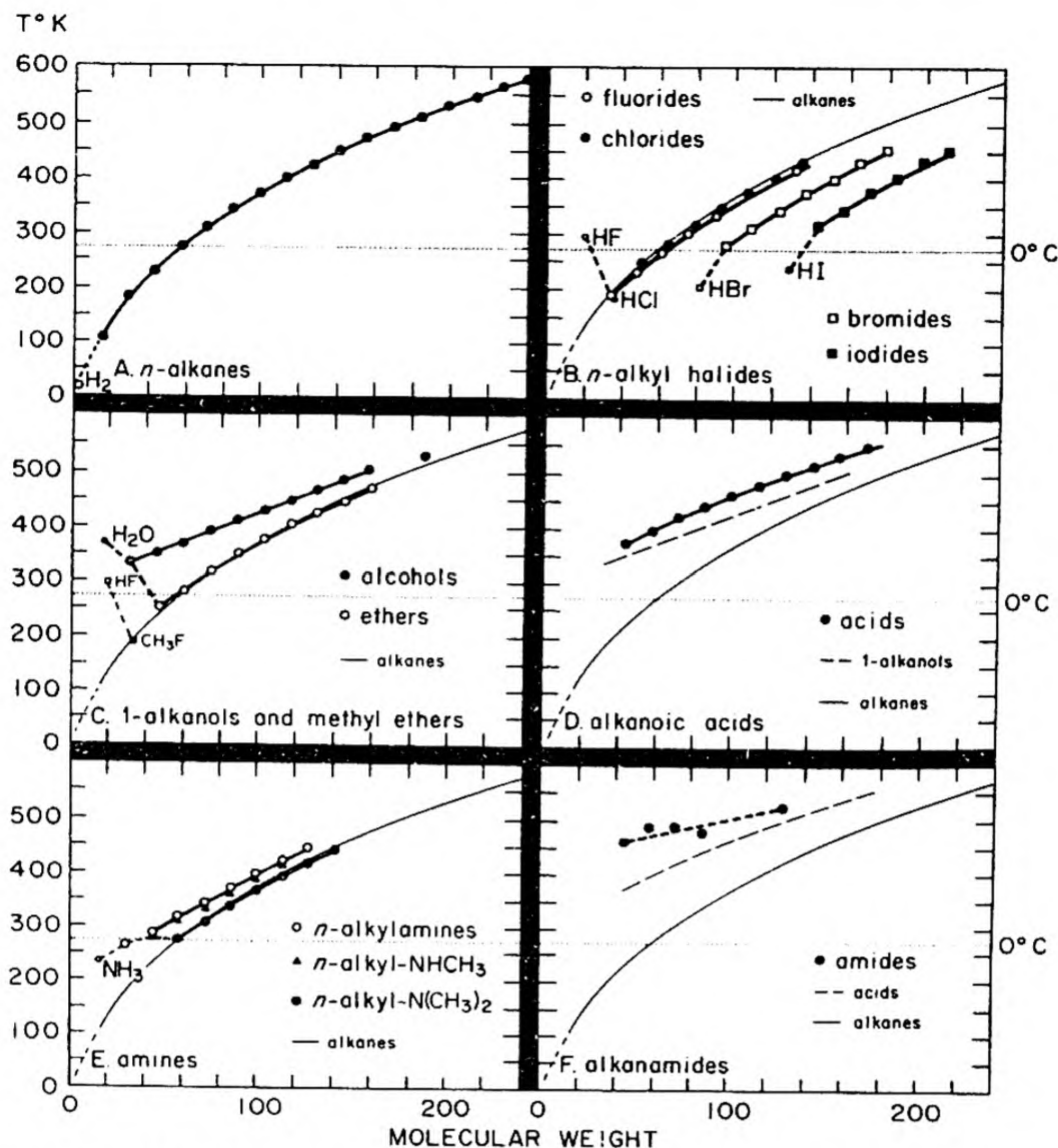


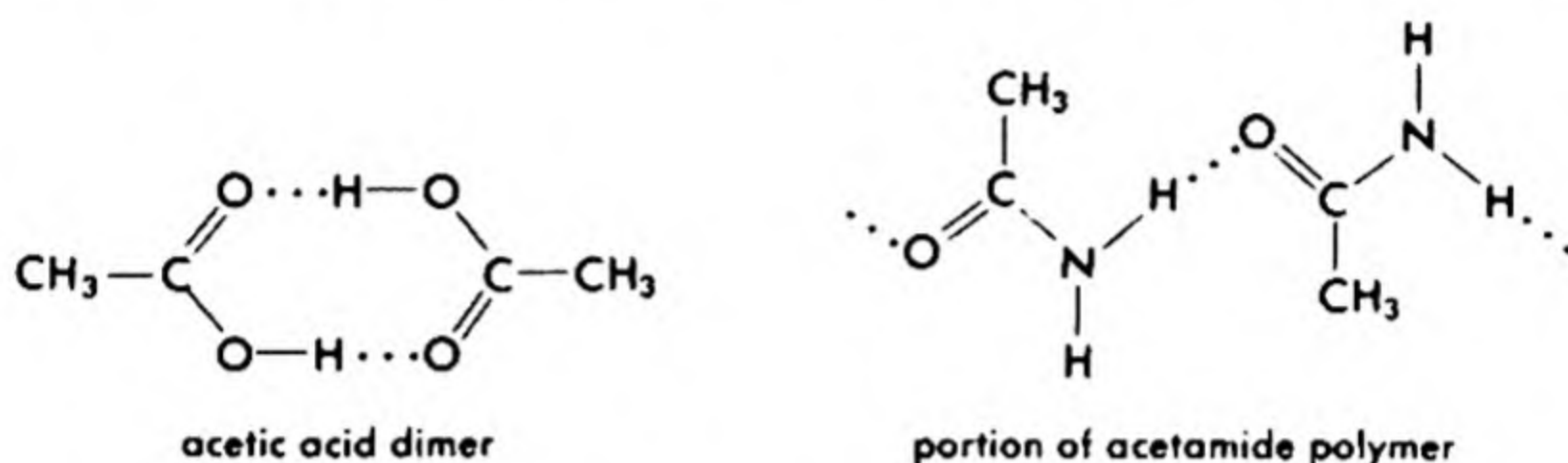
Fig. 9-1. Boiling Points of Various Continuous-Chain Aliphatic Organic Compounds.

point, since the molecules must reach a certain energy content to achieve vapor pressure just in excess of that of the atmosphere.

The consequences of hydrogen bonding are apparent in the boiling points of alcohols (Fig. 9-1C) and primary and secondary amines (Fig. 9-1E) and are especially evident in the boiling points of carboxylic acids, (Fig. 9-1D) and amides (Fig. 9-1F).

Carboxylic acids form hydrogen-bonded dimers, even in relatively dilute solution in nonpolar solvents. The molecular weight of acetic acid

determined by freezing point depression in benzene, for example, is 120, not 60. The structure of the dimer given below has been confirmed by electron diffraction studies (Chapter 36). Dimeric amides could be possible, too, but the presence of the second hydrogen atom on nitrogen, *trans* to the carbonyl oxygen, provides the possibility of formation of chain polymers. These seem to be the preferred form for most amide associations and serve to explain why amides have higher boiling points even than the related carboxylic acids. In the vapor phase, both acids and amides exist partly in monomeric form and partly in associated form.



Simple aldehydes and ketones cannot form hydrogen bonds in their pure states, but are strongly polar, hence show boiling points higher than alkanes, but not as high as those of hydrogen-bonded compounds of the same molecular weights (Fig. 9-2A). Polarity is also responsible for relatively high boiling points of nitriles (Fig. 9-2B). Nitrile polarity effects exceed even the effects of hydrogen bonding in alcohols.

Melting points are conspicuously dependent upon the symmetry and packing qualities of the molecules, as well as their attractive forces. Melting disorganizes a symmetrical array of molecules, in which attractive forces are maximized, to a more random, mobile array. Some work must be done to separate the points of attraction of the favorably oriented

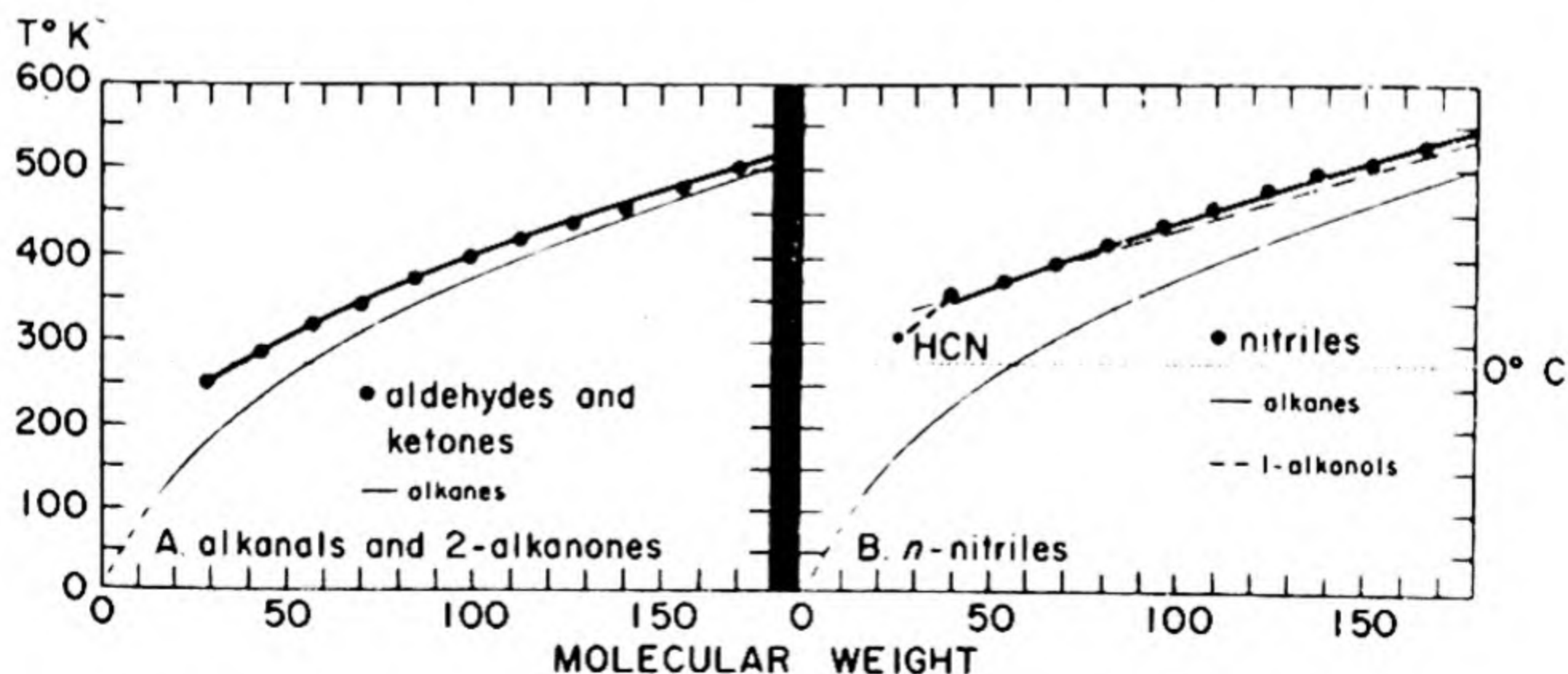
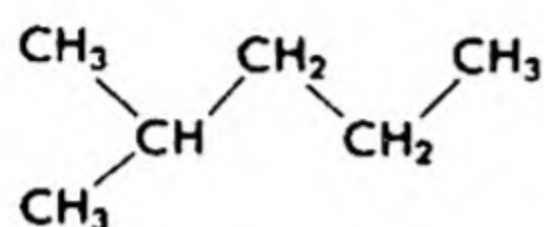


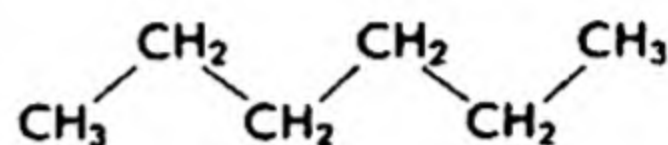
Fig. 9-2. Boiling Points of Continuous-Chain Aldehydes and Nitriles.

molecules as these molecules move to more random positions, even though the overall molecules may not be much farther apart. Again, much of this work influences the heat of fusion, but the melting point is indirectly influenced, since the molecules must achieve a state of thermal agitation sufficient to overcome the attractive forces before disorganization (melting) can occur.

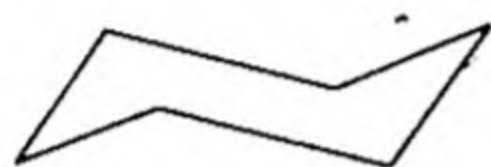
The effects of molecular symmetry are illustrated in the following series, arranged in order of increasing symmetry and compactness of molecules:



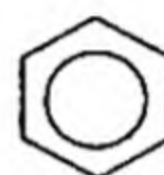
isohexane (119.4°K)



n-hexane (177.8°K)



cyclohexane (279.6°K)



benzene (278.6°K)

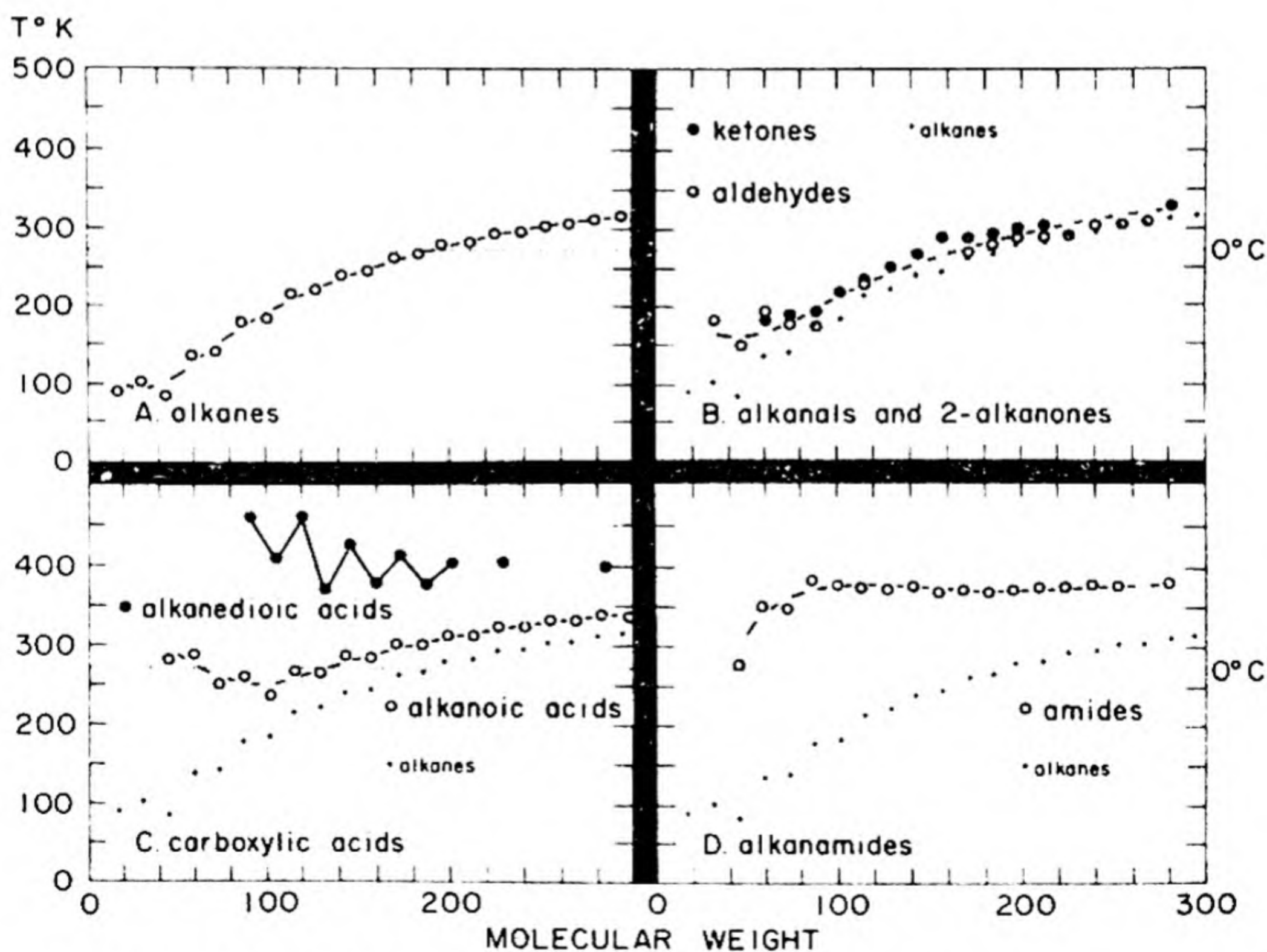


Fig. 9-3. Melting Points of Various Continuous-Chain Organic Compounds

Similar considerations are responsible for the alternation in melting points of normal alkanes (Fig. 9-3A). Even-numbered alkanes, $C_{2n}H_{4n+2}$, pack more closely into a crystal lattice than odd-numbered ones, $C_{2n+1}H_{4n+4}$ (Fig. 9-4). Such alternation is accentuated in compounds with polar or hydrogen-bonding groups (Fig. 9-3B, C, and D). The effect is especially strong in the series of alkanedioic acids (Fig. 9-3C).

B. Solubility in Water

Molecules with weak associative forces easily intermingle. Thus, non-polar, nonhydrogen-bonding molecules are usually highly soluble in each other. Molecules with strong associative forces exclude those with weak associative forces. Penetration of nonassociative molecules into a matrix of strongly interacting molecules, such as water, would involve work in the separation of some of the attractive centers, hence is energetically unfavorable. On the other hand, when there is association between molecules comparable in strength to that between like molecules, intermingling is again energetically favorable and solubility results.

With water as the solvent, the forces that must be matched are strong hydrogen bonding forces between water molecules. Almost the only

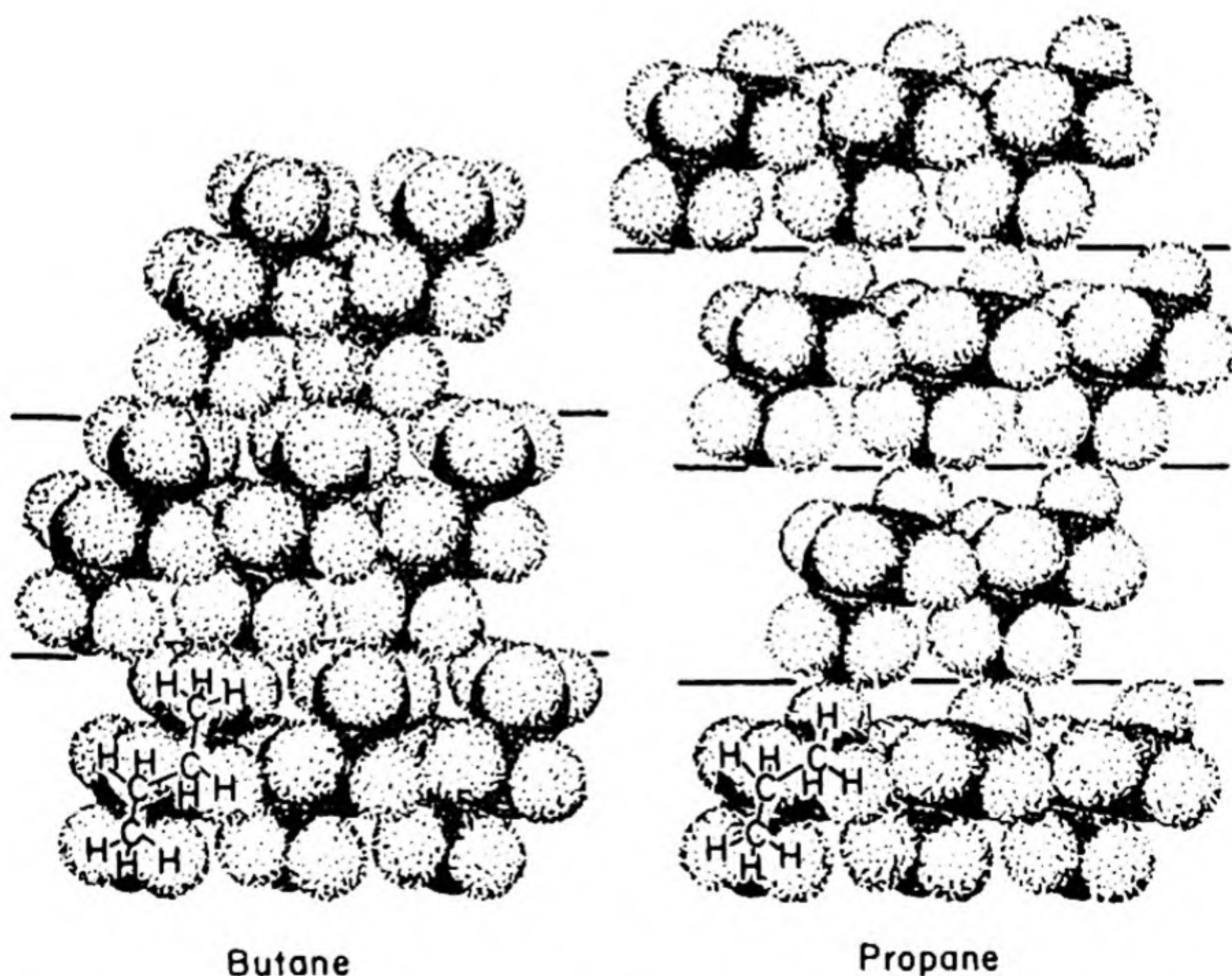


Fig. 9-4. Diagram of Crystal Packing in Even and Odd Hydrocarbon Molecules.

forces strong enough to match these in association between water and other molecules are also hydrogen bonding forces. (If the solute forms ions in water, this also provides strong attractions for water molecules.) Thus, those compounds with atoms (N, O) that can attract the hydrogen ends of water molecules strongly and those with groups (OH or NHR) that can attract the oxygen atoms of water molecules strongly tend to be soluble in water.

Organic molecules contain, as well as hydrogen-bonding groups, non-associative hydrocarbon groups. The larger these hydrocarbon groups, the more associations between water molecules are disrupted to bring the organic molecule into solution, and the greater the tendency to exclude the molecule. Thus, solubility, like other physical properties, is directly related to the overall composition of the solute molecule. In homologous series of monofunctional compounds with hydrogen-bonding groups, the logarithm of the solubility in water is linearly related to the molecular weight (eq. 1).

$$(1) \quad \log s = a - bn$$

s = solubility, moles/liter

a and b = constants

n = number of carbon atoms in a solute molecule

At 20°, $a = 2.7 \pm 0.2$ and $b = 0.65$ for liquid alcohols, ethers, aldehydes, ketones, carboxylic acids, and amides with unbranched chains. Typical solubility relationships are given in Fig. 9-5.

When the solid phase is in equilibrium with the dissolved phase, intracrystalline forces complicate the relationship. The alkanedioic acids with even numbers of carbon atoms pack more tightly in the crystalline state than those with odd numbers of carbon atoms (see §9-1A). This results in separate logarithmic relationships for the even series and the odd series, in which the odd-membered acids are much more soluble at comparable molecular weights than the even (Fig. 9-5C).

9-2 BRIEF SURVEY OF CONSTITUTIVE PROPERTIES

A good background in physics is desirable for a rigorous treatment of such constitutive properties as dipole moments and spectra. However, these properties are of fundamental value to a study of organic compounds and their reactions. Therefore, these topics are introduced briefly here, with minimum theoretical discussion, so that data obtained by instrumental methods can be utilized where appropriate. Unit IV, which comes late enough in the book to allow experience with principles of physics to intervene, goes more deeply into these topics and discusses their theory and their instrumentation.

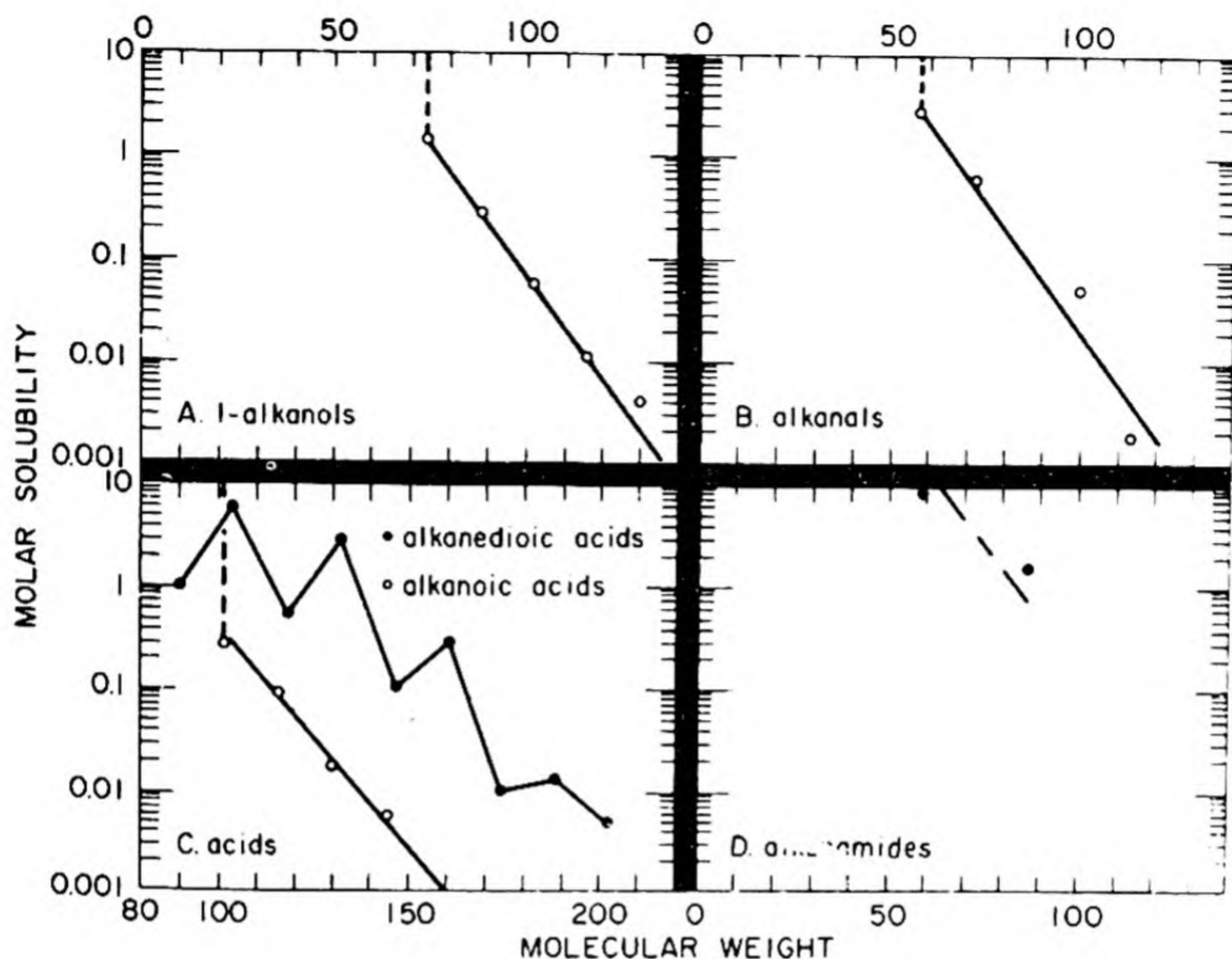


Fig. 9-5. Solubilities of Various Continuous-Chain Organic Compounds in Water at 20°.

A. Electromagnetic Absorption Spectra

Two types of spectra of molecules are of great value to the organic chemist. One type occurs in the ultraviolet to visible region of electromagnetic radiation (wavelengths of 200–800 millimicrons, $m\mu$), the other in the infrared region (2–16 microns, μ). The 200–800 $m\mu$ region includes absorption spectra due to electronic transitions. These are energy changes in a molecule in which an electron is excited from a ground-state MO to a higher-energy unoccupied MO.

One of the most common absorbance transitions in this region is the $n \rightarrow \pi^*$ transition of a multiple bond. In this, an unshared electron on one of the atoms at a multiple bond is excited to the lowest unoccupied π^* MO. Since many energy levels of molecular vibrations are associated with each electronic state, the spectra obtained are band spectra, not line spectra, which are read on the instrument as a series of "peaks" and "valleys." Fig. 9-6 shows the ultraviolet spectrum of acetone. The absorbance around 280 $m\mu$ is due to an $n \rightarrow \pi^*$ transition. The wavelength of the maximum of absorbance is related to the transition energy for the electronic excitation and the intensity of absorbance is related to the con-

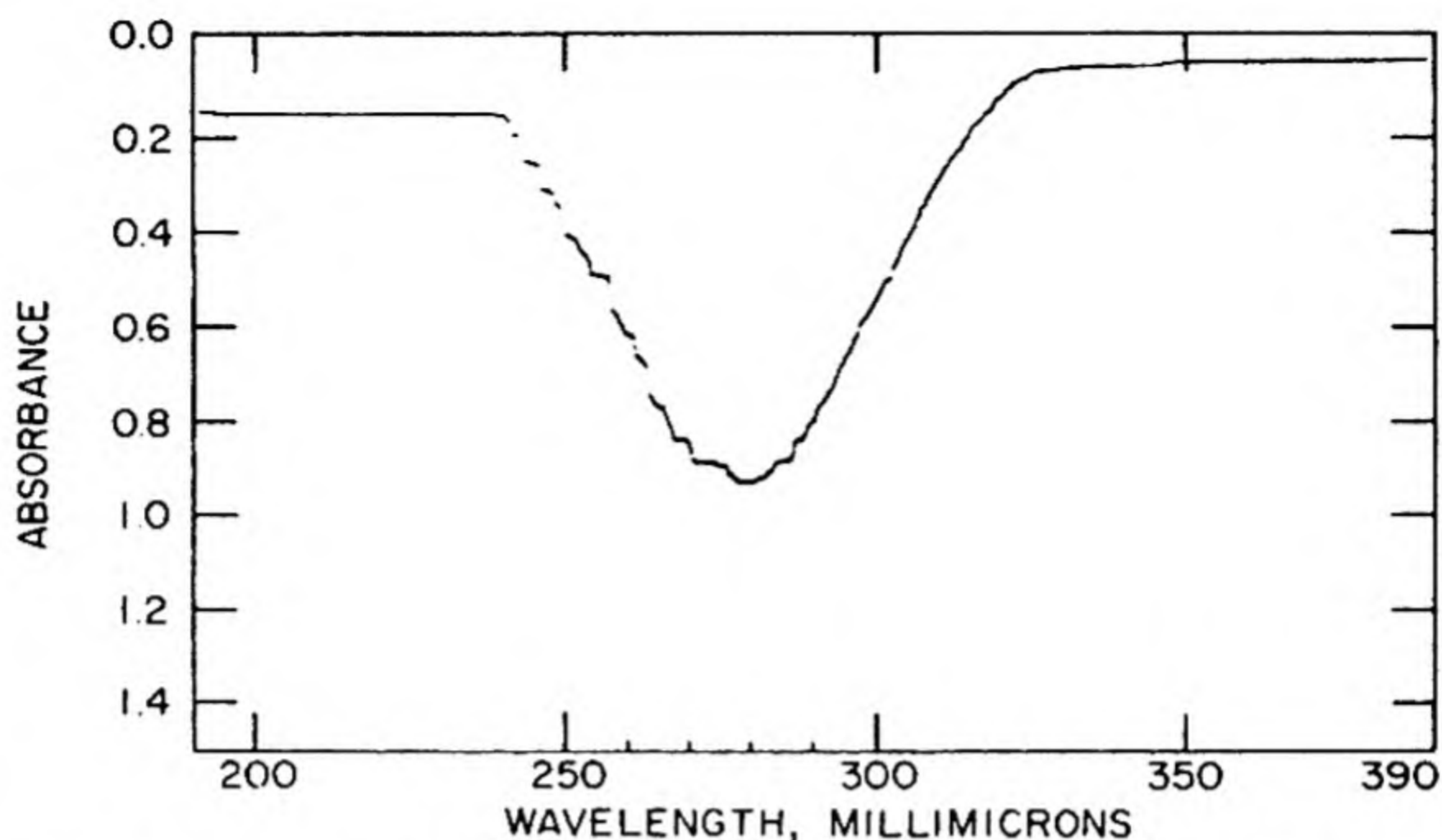
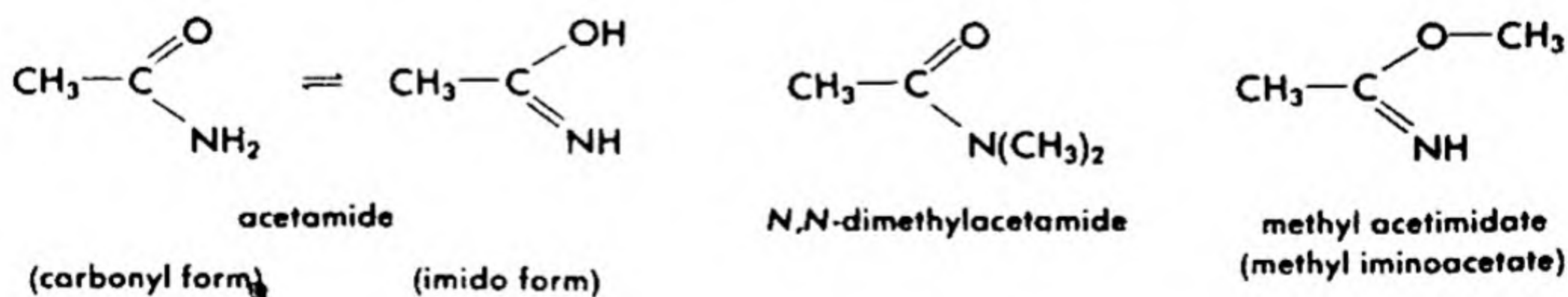


Fig. 9-6. Ultraviolet Absorption Spectrum of Acetone, 0.5% in Cyclohexane.

centration of electrons which undergo the transition. After solution concentration effects are taken into consideration, the intensity of absorbance is related to the probability that the transition will occur upon interaction of the susceptible group with a photon of the correct energy and to the number of susceptible functions in the molecule. For example, 2,5-hexanedione absorbs more strongly than acetone at the carbonyl frequency because the former has twice the number of carbonyl groups.

Ultraviolet spectra of closely similar structures are similar and can be used to show structural analogies. For example, the ultraviolet spectrum of tautomeric acetamide resembles that of nontautomeric dimethylacetamide more than it does that of methyl acetimidate. For this reason, acetamide is considered to be mainly the carbonyl form, with only very minor amounts of the imido form at equilibrium with it.



Spectra in the infrared region are of an entirely different nature. These lower-energy transitions involve only atomic motions, not electron levels. The region commonly used for structural verification detects vibrational energy changes, somewhat broadened by the several rotational energy levels associated with each vibrational level.

Infrared spectra are generally easier to interpret than ultraviolet spectra,

since the characteristic bands for vibrational transitions overlap less than those for electronic transitions. Some typical infrared spectra for simple representatives of several classes of compounds are given in Fig. 9-7. A correlation chart (chart of correlations between absorption maxima and groups) is provided in Fig. 9-8. Infrared spectra are now simple to obtain and are widely used to identify organic compounds and substantiate their structures.

The equilibrium position in the tautomerism of amides and related problems are easier to solve by infrared than by ultraviolet, as reference compounds are unnecessary. The N—H and O—H stretching frequencies are far enough apart to be readily distinguishable. Only at high concentration is there a detectable OH band in dry acetamide, which confirms the carbonyl structure as the prevalent one.

Even structural features as fine as conformational interconversions can be detected by infrared studies. 1,2-Dibromoethane shows more absorption bands in the liquid state than in the solid state. This has been interpreted as indicating that solid 1,2-dibromoethane exists in *anti* conformation, whereas liquid 1,2-dibromoethane equilibrates between *anti* and *gauche* conformations. The latter conformation has less symmetry, hence more degrees of freedom, and more bands than the *anti*.

B. Proton Magnetic Resonance

Spectra due to the energy transitions of atomic nuclei which are induced to tip over in a magnetic field are called *nuclear magnetic resonance* (NMR) spectra. Of these nuclear magnetic studies, proton magnetic resonance (PMR) is the most widely used and, at present, the most useful.

The chemical environment of a hydrogen nucleus affects its magnetic shielding. Thus, hydrogen atoms attached to different atoms or to atoms bonded to different groups have different responses to the magnetic field strength. These *chemical shifts* depend on the magnitude of the magnetic field. Correlations at 14,092 gauss, with tetramethylsilane as reference, are given in Fig. 9-9.

Hydrogen atoms on adjacent atoms and, less strongly, those on atoms attached in other specific relative positions, interact to cause *spin splitting* of their spectral lines. The magnitude of such splitting is independent of magnetic field, but depends on the proximity and orientation of the coupled protons. The sensitivities of the chemical shift and spin splitting to molecular structure and molecular conformations make NMR a very powerful tool for structural determination and structural analysis. Some examples of NMR spectra of simple compounds are given in Fig. 9-10.

C. Dipole Moments

The polar nature of a compound receives quantitative measure in terms of the *dipole moment*. This is the magnitude of electronic charges in a

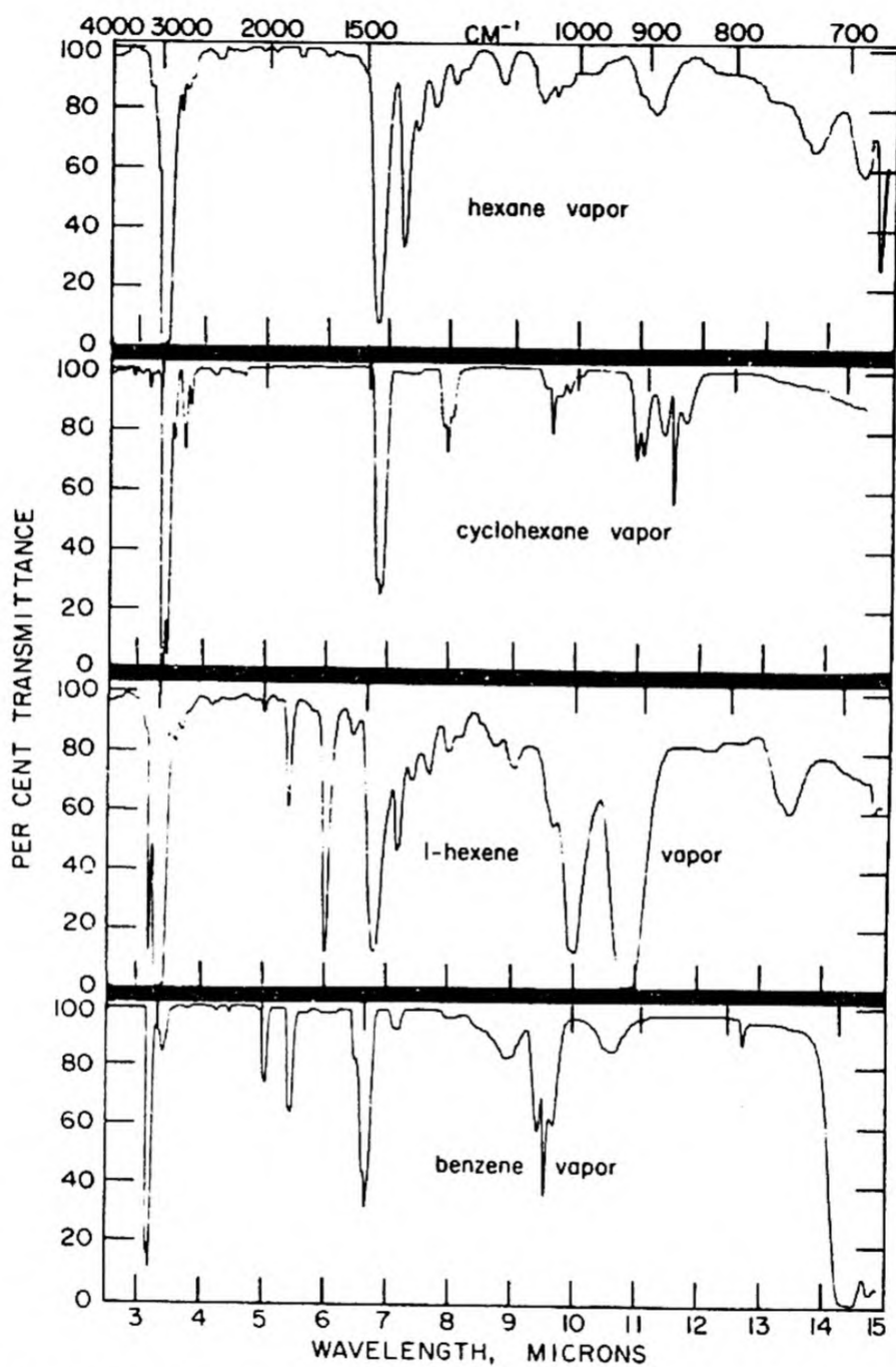


Fig. 9-7. Infrared Absorption Spectra of Various Organic Compounds

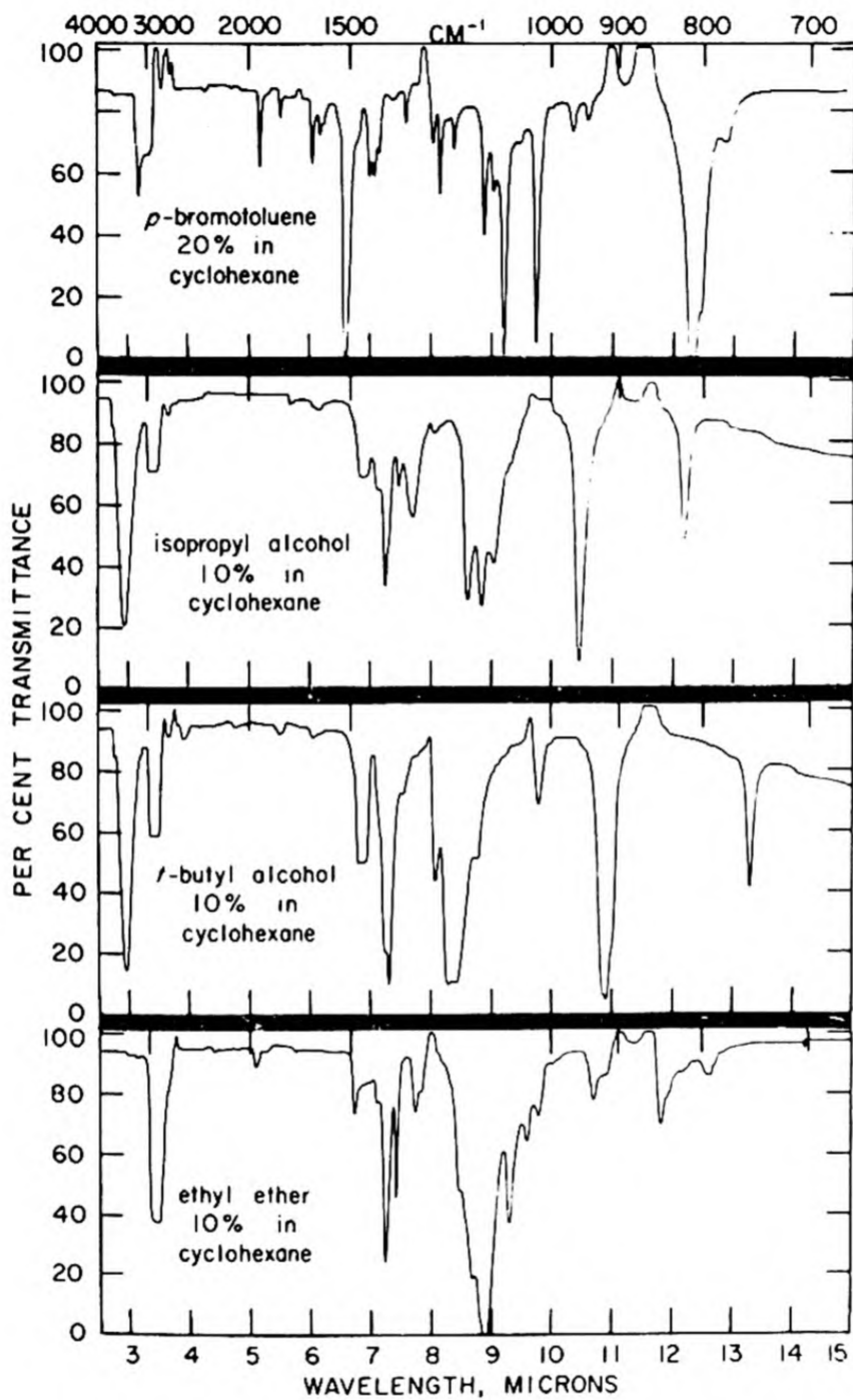


Fig. 9-7 (Continued)

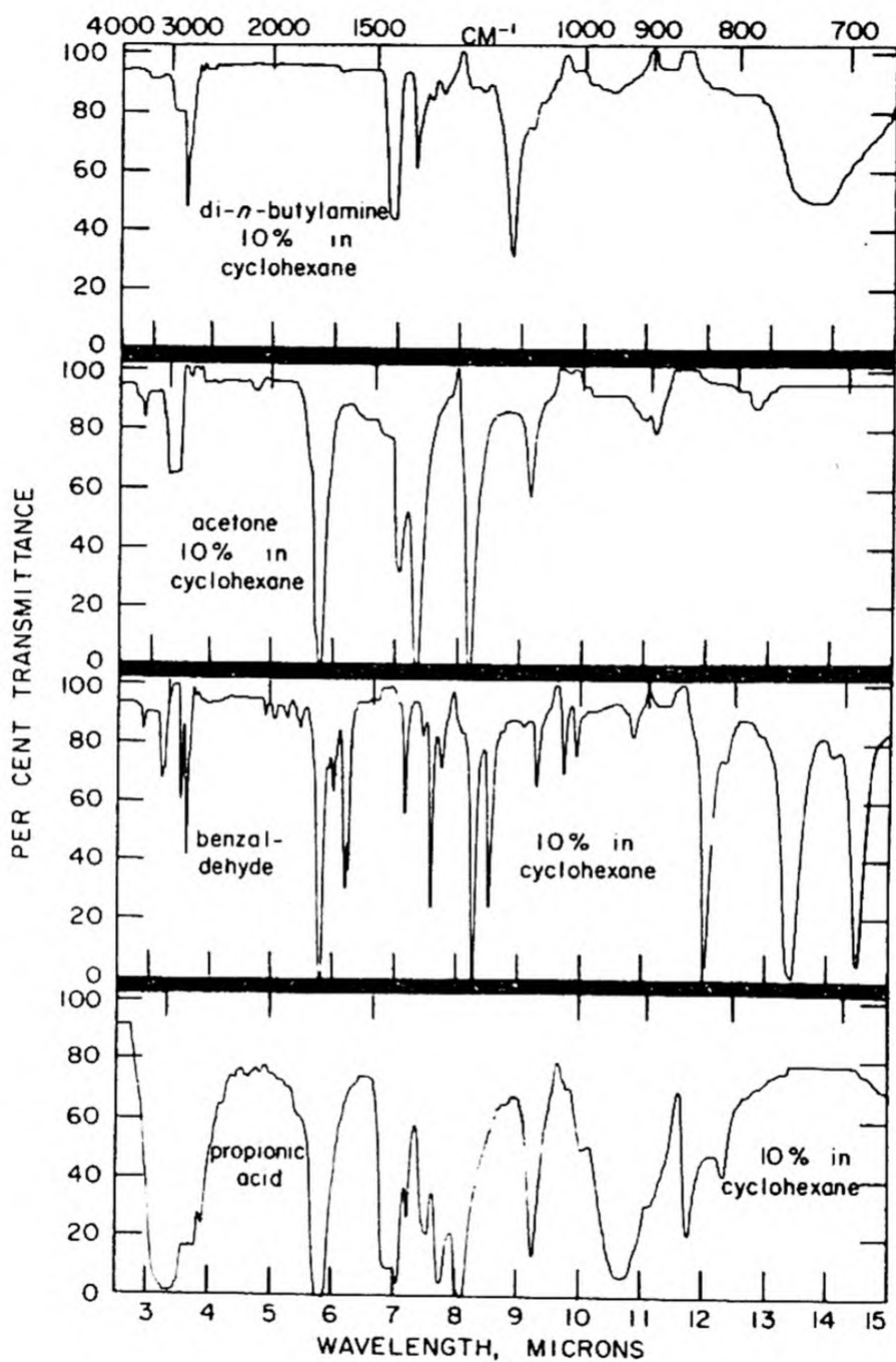


Fig. 9-7 (Continued)

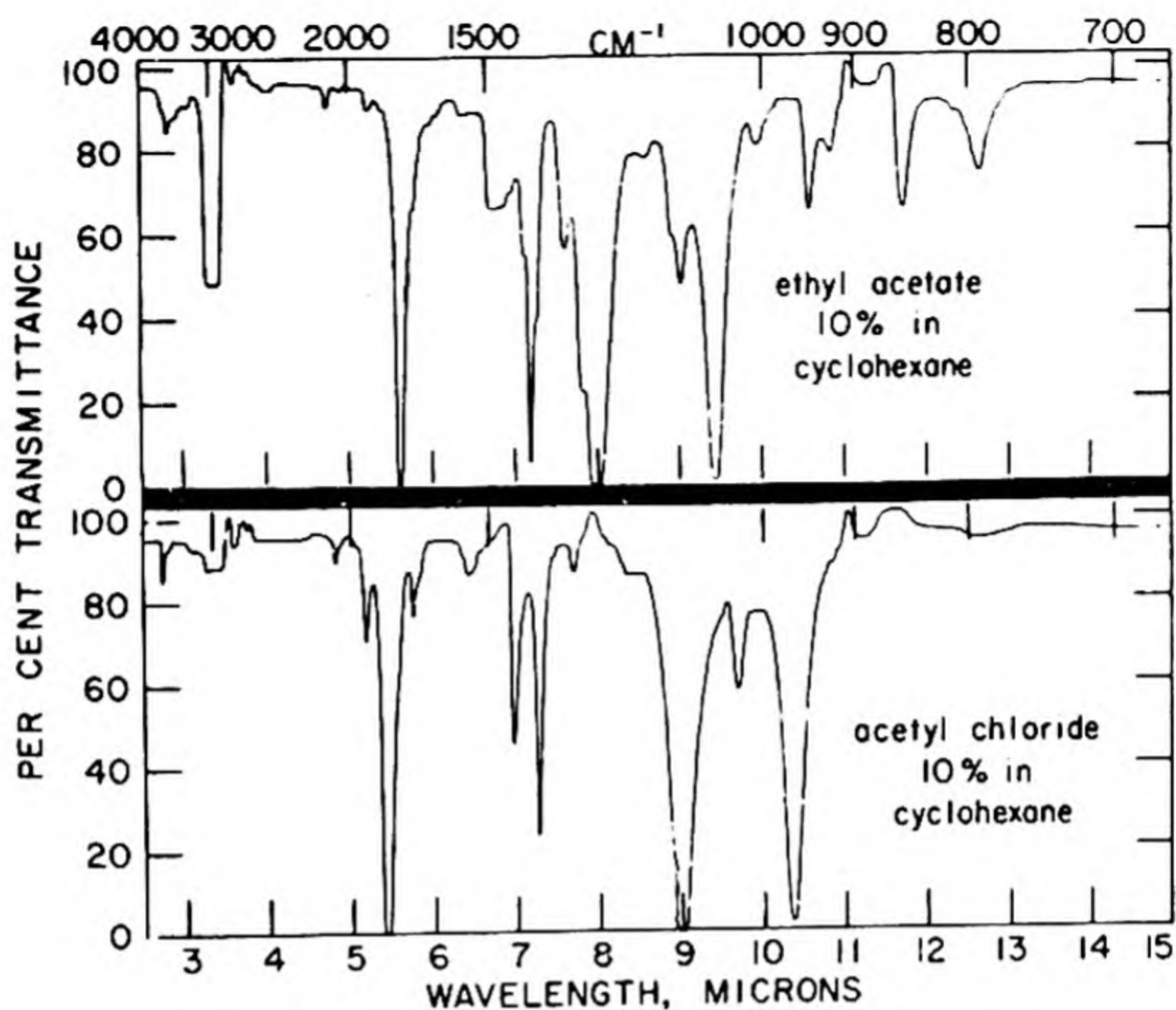


Fig. 9-7 (Continued)

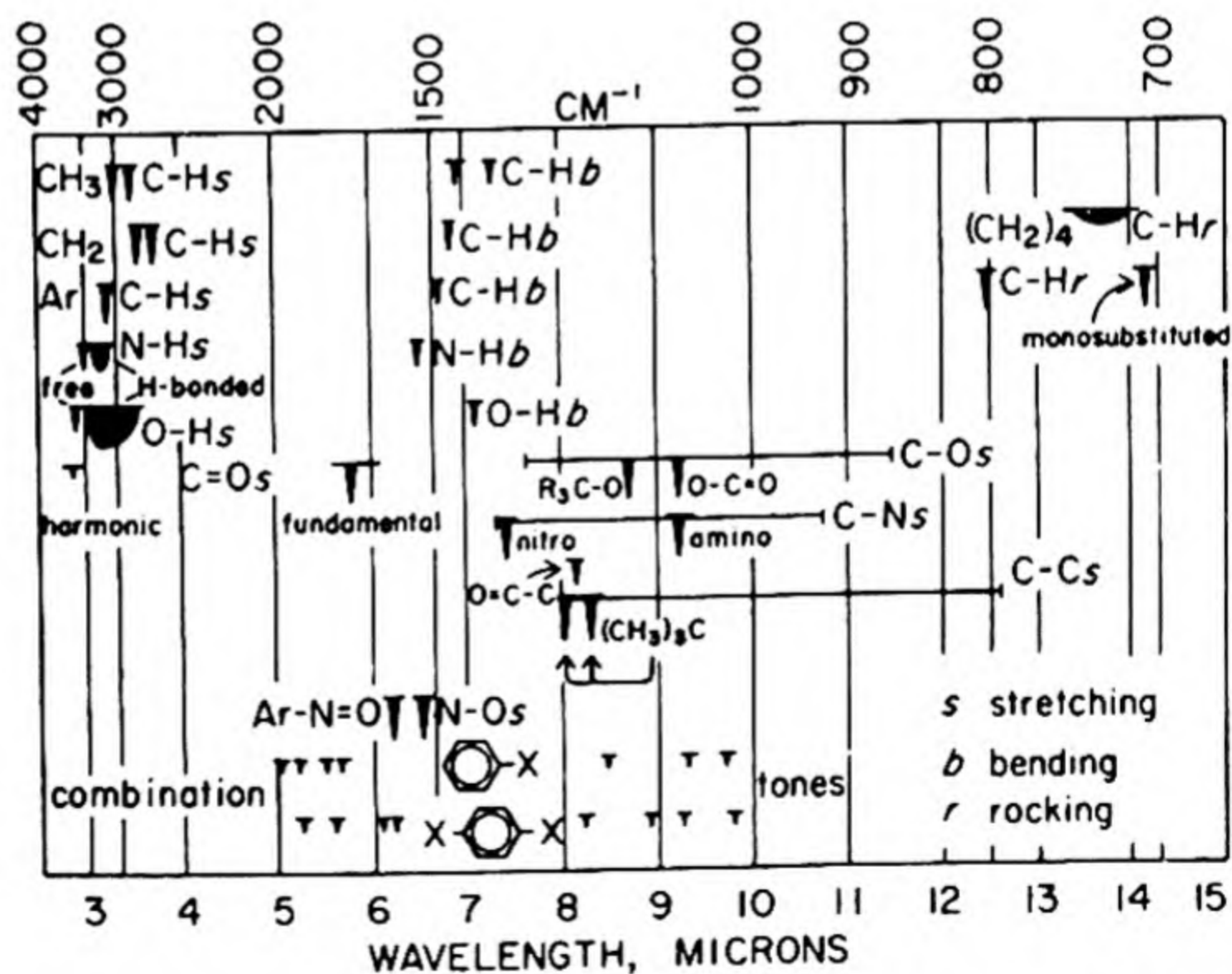


Fig. 9-8. Correlation Chart for Infrared Spectra—in same wavelength scale as preceding spectra.

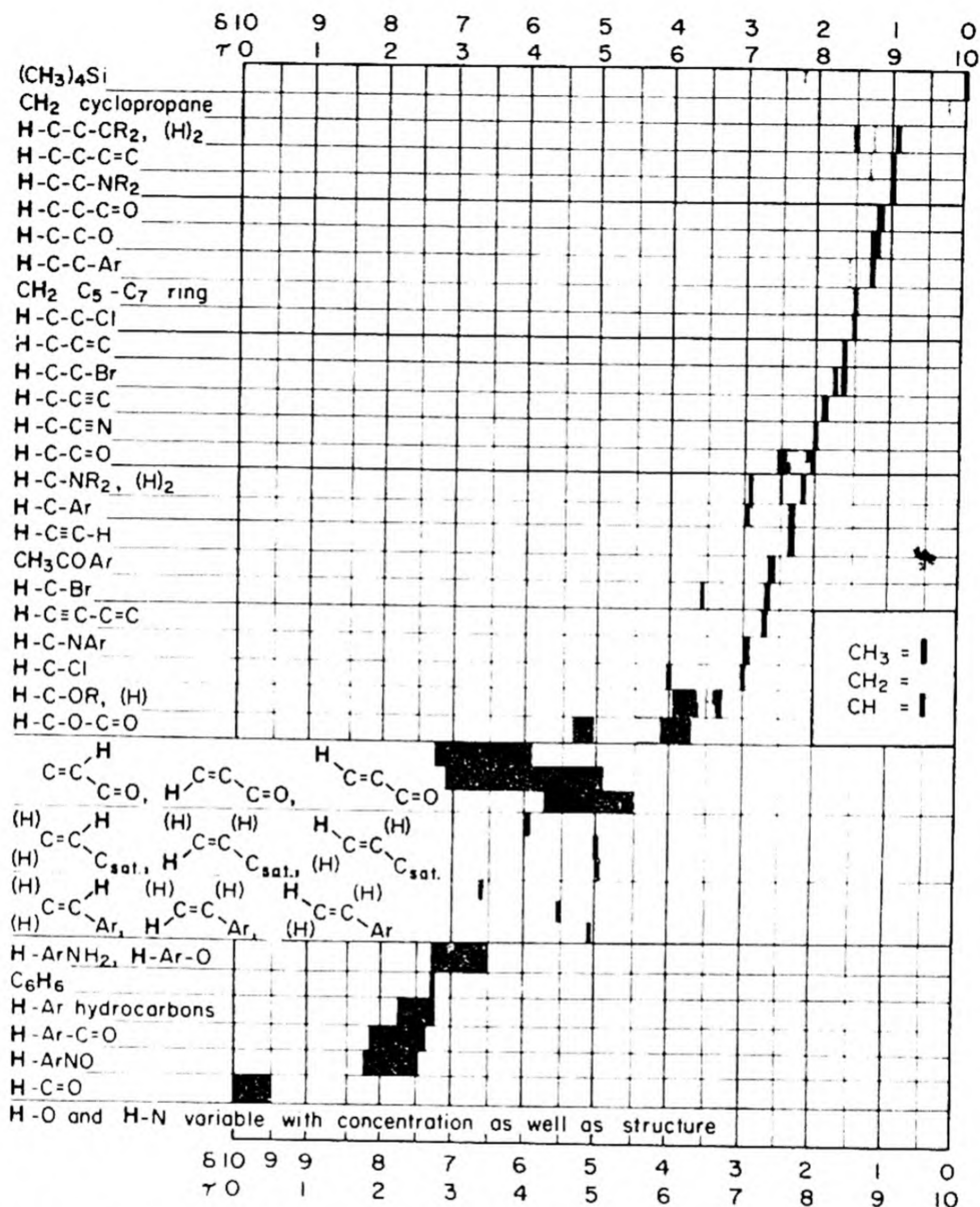


Fig. 9-9. Correlation Chart for NMR Spectra. Marks represent centers of chemical shift locations of peaks or ranges of chemical shift.

molecule multiplied by the distance that separates them. Units are electrostatic units (e.s.u.) \times cm. $\times 10^{18}$ = Debyes (D.). Dipole moments are vector forces, that is, directional quantities. The molecular dipole moment is the vector sum of the group moments which are present in the molecule.

These group moments are, in comparable situations, constant, so that molecular dipole moments give significant information about bond angles. However, resonance interactions, conformational transformations, and induced dipoles introduce complicating factors that make bond angle calculations very uncertain. Conversely, however, if one assumes reasonable bond angles, the deviations from simple treatment can be used

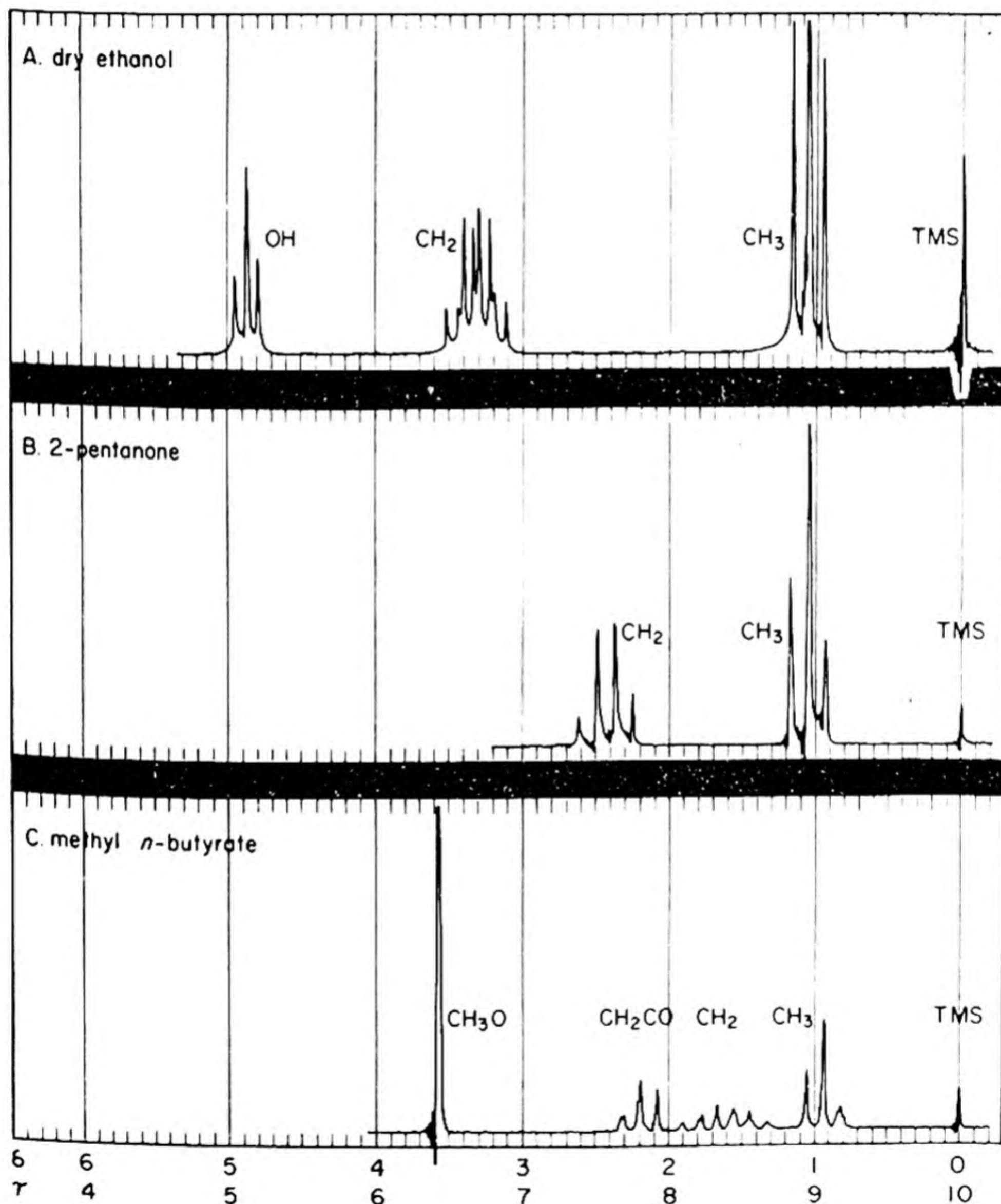
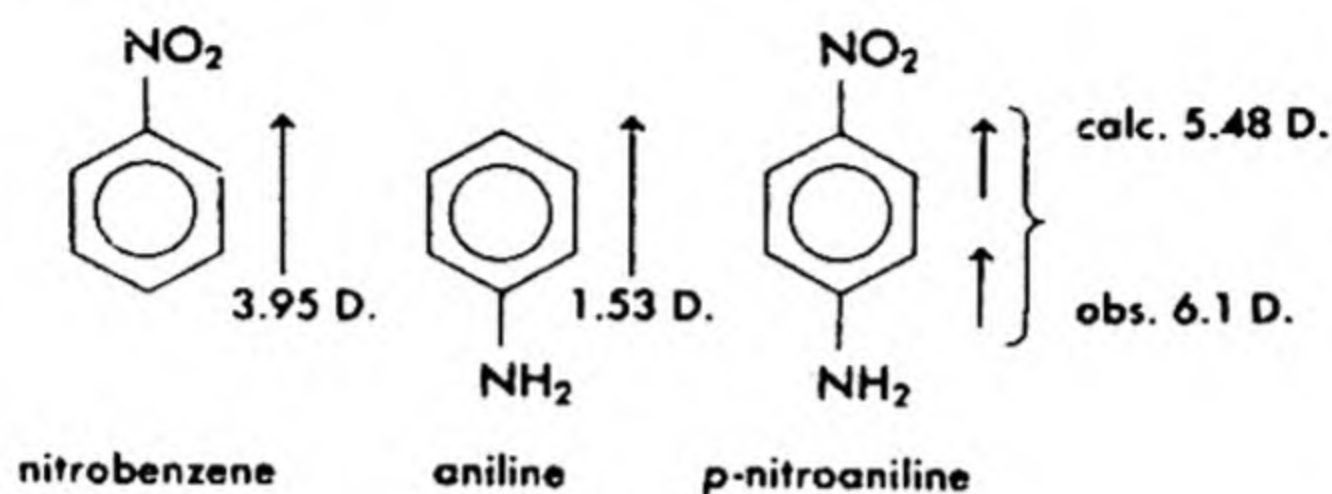


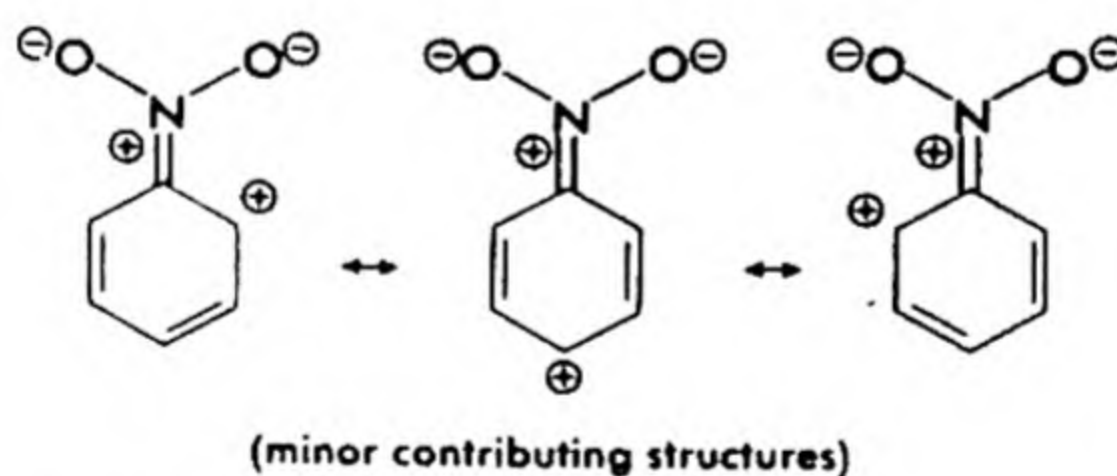
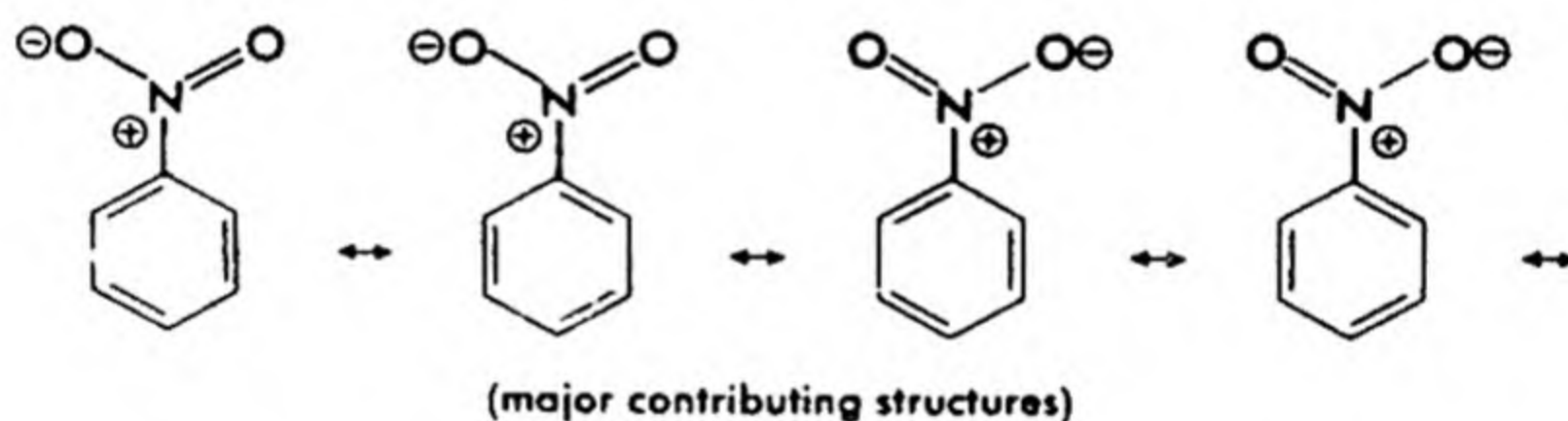
Fig. 9-10. NMR Spectra of Representative Organic Compounds not to same scale as correlation chart.

to estimate the degree of resonance interaction or freedom of conformational interconversions in the respective situations.

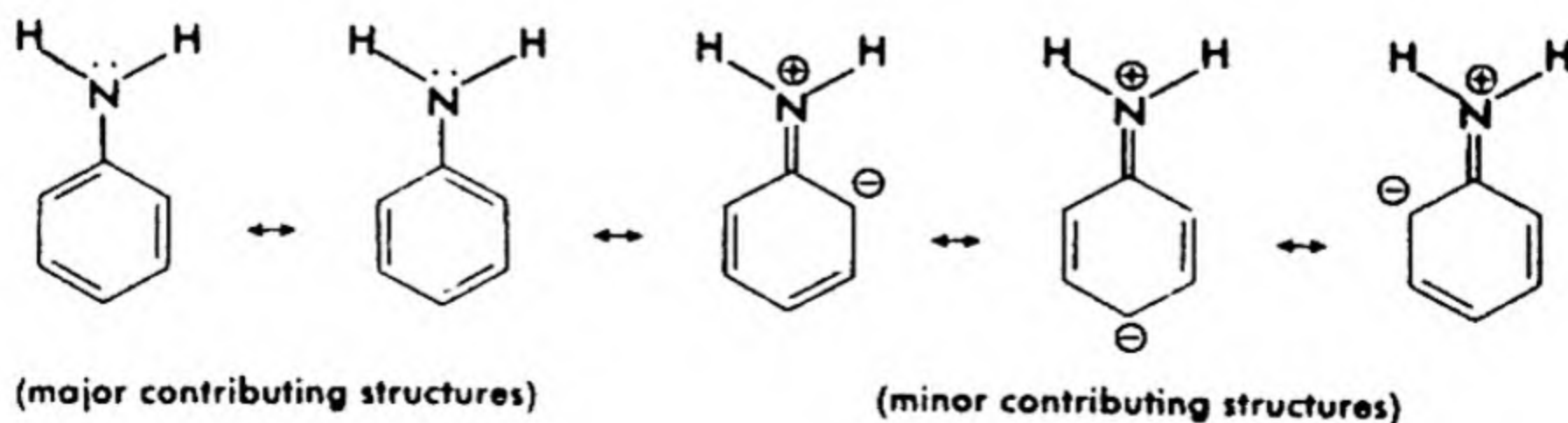
For example, nitrobenzene, aniline, and *p*-nitroaniline have dipole moments, respectively, of 3.95 D., 1.53 D., and 6.1 D. The dipole moment of *p*-nitroaniline exceeds the calculated value of 5.48 D. ($3.95 + 1.53$, since both the NO_2 group moment and the NH_2 group moment point in the same direction) by 0.62 D., a value larger than the experimental error. This indicates resonance interaction between the amino group and nitro group through the benzene ring which is above and beyond the resonance interactions these groups have independently with the ring in the mono-functional compounds.

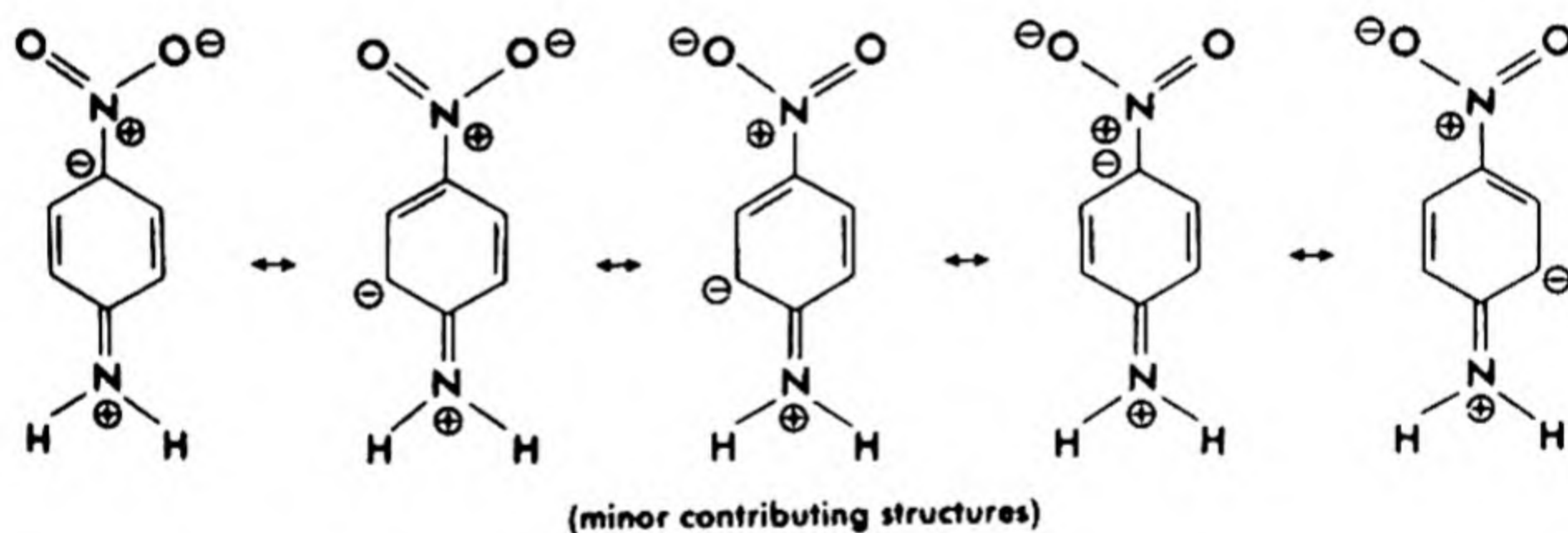
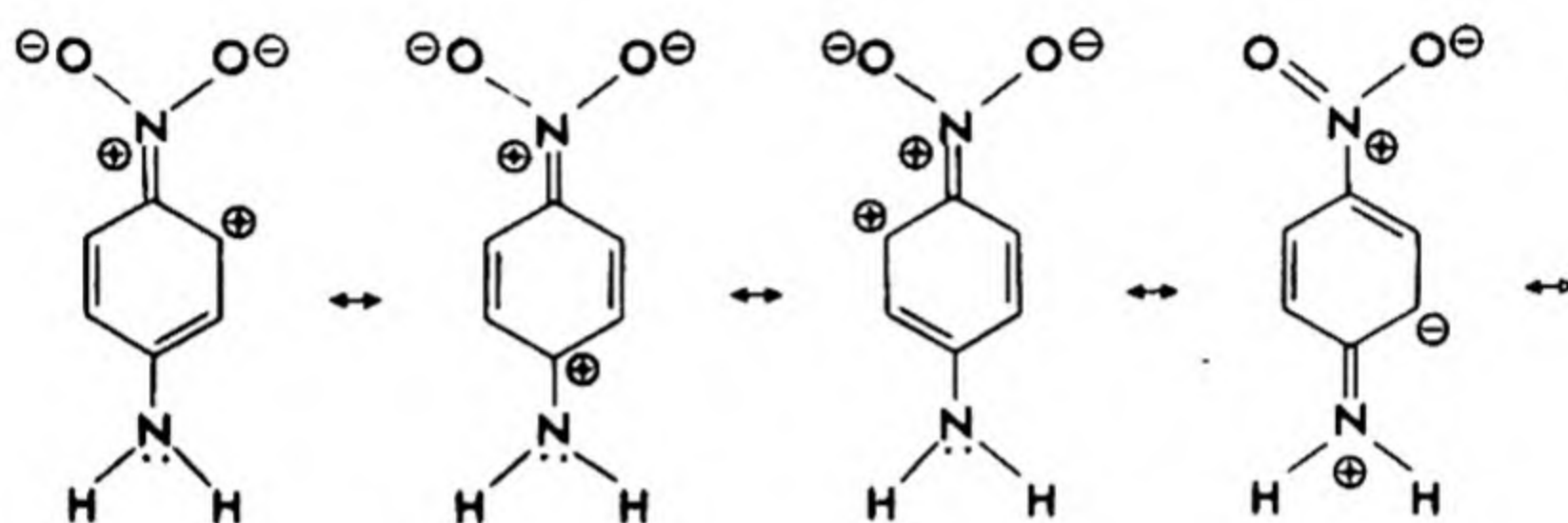
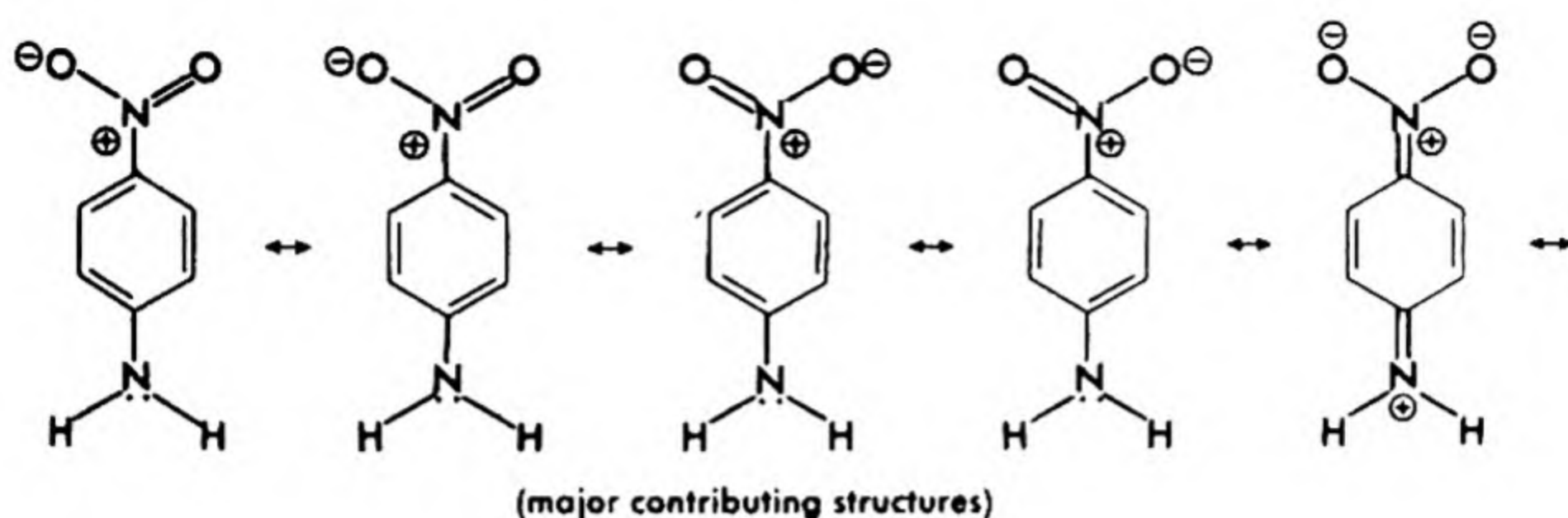


Valence-bond interpretation of resonance in nitrobenzene



Valence-bond interpretation of resonance in aniline



Valence-bond interpretation of resonance in p-nitroaniline

The evidence for resonance interaction from dipole moments contributes to the interpretation of rates of reactions in substituted benzene derivatives.

SUPPLEMENTARY READINGS

- Barrow, G. M., *The Structure of Molecules*, Benjamin, New York, 1963, Chapters III and V.
- Dyer, J. R., *Applications of Absorption Spectroscopy of Organic Compounds*, Prentice-Hall, Englewood Cliffs, N. J., 1969.
- Mohacsi, E., "Characteristic NMR Spectral Positions for Hydrogen in Organic Structures," *J. Chem. Educ.* **41**, 38 (1964).

- Pimentel, G. C., and A. L. McClellan, *The Hydrogen Bond*, Freeman, San Francisco 1959, Chapters 1, 2, and 6.
- Silverstein, R. M., and G. C. Bassler, "Spectrometric Identification of Organic Compounds," *J. Chem. Educ.* **39**, 546-553 (1962).
- Stevenson, P. E., "The Ultraviolet Spectra of Aromatic Hydrocarbons; Predicting Substitution and Isomer Changes," *J. Chem. Educ.* **41**, 234-239 (1964).

QUESTIONS AND PROBLEMS

1. Why is there considerable variation in the solubility of oxygen derivatives of hydrocarbons (i.e., alcohols, ketones, acids, etc.) in water? How do physical properties differ from chemical properties in their dependence on molecular structure?
2. Explain on the basis of molecular structure why 1-butanol has a lower boiling point than ethylene glycol, but a higher boiling point than *n*-butyraldehyde.
3. Explain why boiling points of carboxylic acids are so high compared with hydrocarbons or alcohols of similar molecular weight.
4. Why is it possible for nitriles to form strong hydrogen bonds with water, but not in the pure state among the nitrile molecules?
5. Explain on the basis of molecular forces the relationship between the number of hydrogen atoms on the nitrogen atom in an amine and the boiling point of an amine, other factors being equal.
6. Would the number of hydrogen atoms on the nitrogen atom of an amine be expected to affect its solubility in water greatly? Why? After answering this, look up the solubilities of *n*-hexylamine, di-*n*-propylamine, and triethylamine in water. Was the change in solubility what you expected? What factor other than hydrogen bonding is involved? Now compare the solubilities of *N*-methylaniline and *o*- or *p*-toluidine. Is your original hypothesis supported by these data? Why?

REVIEW QUESTIONS AND PROBLEMS

1. Make a table listing reagents down the left side and compound classes across the top, as illustrated in the partial table below. Use several sheets of paper for your table so that there is room in the spaces for what is to be included. The dividing lines in the list of classes below indicate the number of lines to be drawn dividing classes in the table. Closely related classes are separated by single lines; less closely related classes which belong in a general category are separated by double lines, and unrelated classes are separated by triple lines. Include the following classes of compounds:

1. Hydrocarbons

Alkanes

Alkenes

Inner alkynes

1-Alkynes

Arenes

Small ring cycloalkanes

2. Halides

Alkyl

Aryl and vinyl

3. Hydroxy compounds

Alcohols

Phenols

4. Ethers

5. Carbonyl compounds

Aldehydes

Ketones

Quinones

6. Carboxylic acids

7. Acid derivatives

Esters

Anhydrides

Acyl halides

8. Amines

9. Acid ammono derivatives

Amides

Nitriles

10. Nitro compounds (aromatic)

Include the following general reagents:

1. Water
2. Dilute hydrochloric acid
3. Concentrated sulfuric acid
4. Dilute sodium hydroxide
5. Dilute sodium bicarbonate solution
6. Bromine in carbon tetrachloride
7. Dilute potassium permanganate
8. Sodium metal

PARTIAL TABLE

	Hydrocarbons					
	Alkanes	Alkenes	Alkynes	1-Alkynes	Arenes	Small-ring
Water	Insoluble					
Dil. HCl	NR					
Conc. H ₂ SO ₄	NR					
Dil. NaOH						
Dil. NaHCO ₃						
Br ₂ + CCl ₄		Fast decol. $\begin{array}{c} \text{Br} \\ \\ \diagup \text{C} - \text{C} \diagdown \\ \\ \text{Br} \end{array}$				
KMnO ₄						
Na						
Group and special reagents				Ag(NH ₃) ₂ ⁺ : gray ppt. R-C≡C-Ag	H ₂ SO ₄ + SO ₃ :	

It is recommended that you fill in the table as you study Unit II and as you observe the behavior of compounds in the laboratory. In the line after each general reagent, indicate any observable change and the formula of the organic product when reaction occurs. If no reaction occurs, indicate NR except after

water. In the water row indicate whether compounds of less than five carbon atoms are soluble if no reaction occurs.

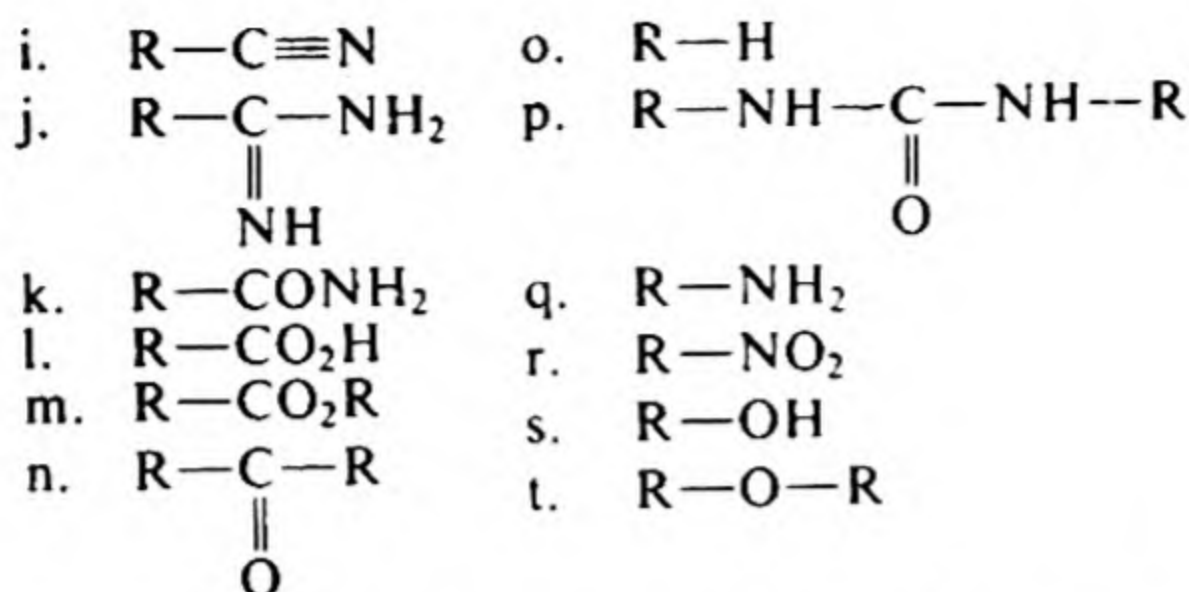
After group and special reagents list those reagents which give characteristic reactions with particular functional groups, with individual classes of compounds, or with individual compounds. Reagents already listed as general reagents need not be repeated unless different concentrations than those indicated are used. Together with the formula of the reagent, give the observed behavior and the formula of the organic product. When subclasses or individual members of a class are involved, indicate what the test shows when positive and what structural feature is responsible for the test.

2. Write an explanation, illustration, or definition to show clearly what is meant by each of the following terms. Diagrams may be used, but should be accompanied by verbal explanation.

- | | |
|-----------------------------|-----------------------------|
| a. addition | z. mesomerism |
| b. alkane | aa. <i>meta</i> |
| c. alkene | ab. molecular configuration |
| d. alkyne | ac. molecular conformation |
| e. arene | ad. molecular formula |
| f. axial | ae. molecular orbital |
| g. boiling range | af. molecular structure |
| h. bond angle | ag. multiple bond |
| i. bond dissociation energy | ah. nitrile |
| j. bond distance | ai. nucleophile |
| k. carbocycles | aj. organic compound |
| l. carbon chain isomers | ak. <i>ortho</i> |
| m. <i>cis-trans</i> isomers | al. <i>para</i> |
| n. crystallization | am. pi orbital |
| o. distillation | an. polar molecule |
| p. electrophile | ao. positional isomers |
| q. equatorial | ap. quinone |
| r. extraction | aq. resonance |
| s. functional isomers | ar. secondary carbon atom |
| t. group | as. sigma orbital |
| u. homologs | at. structural formula |
| v. hybridization | au. substitution |
| w. hydrogenation | av. tautomers |
| x. hydrogen bond | aw. tertiary amine |
| y. melting point | ax. valence bond structures |

3. Write the structural formula of a specific compound representing each of the following classes of compounds. Write the common name and IUPAC name for each compound. Give the name of the class of each compound.

- | | |
|------------------------|--------------|
| a. ArCl | e. R—Br |
| b. ArH | f. R—C≡C—R |
| c. ArOH | g. R—CH=CH—R |
| d. ArSO ₃ H | h. R—CH=O |



4. Write equations for reactions that illustrate the following terms. Use structural formulas of actual compounds.

- | | |
|----------------|---------------------|
| a. combustion | d. sulfonation |
| b. dehydration | e. Wöhler synthesis |
| c. Dow process | f. Wurtz reaction |

5. Write equations for any reactions which occur between each of the compounds listed below and (1) cold, dilute hydrochloric acid, (2) hot, dilute hydrochloric acid, and (3) hot, concentrated hydriodic acid. Use structural formulas for organic compounds.

- | | |
|---------------------------|------------------------------|
| a. 1-butanol | i. <i>n</i> -butylamine |
| b. 4-ethylphenol | j. triphenylamine |
| c. <i>n</i> -propyl ether | k. propanamide |
| d. butanone | l. cyclohexanecarbonitrile |
| e. benzoic acid | m. <i>N,N'</i> -diphenylurea |
| f. acetic anhydride | n. phthalimide |
| g. pentanoyl chloride | o. 2-hydroxypropanenitrile |
| h. ethyl propionate | |

6. Write equations for any reactions which occur between each of the following compounds and (1) cold, concentrated sulfuric acid and (2) hot, concentrated sulfuric acid. Use structural formulas for organic compounds.

- | | |
|-------------------|--------------------|
| a. methanol | f. sodium benzoate |
| b. 1-propanol | g. phenetole |
| c. 2-propanol | h. formic acid |
| d. phenol | i. acetanilide |
| e. 2-butoxyhexane | j. urea |

7. Write equations for any reactions which occur between each of the following compounds and (1) cold, dilute sodium bicarbonate, (2) cold, dilute sodium hydroxide, (3) hot, dilute sodium hydroxide, and (4) hot, fused sodium hydroxide. Use structural formulas for organic compounds.

- | | |
|----------------------------|-----------------------|
| a. 2-chloro-3-methylbutane | e. methyl hexanoate |
| b. chlorobenzene | f. pentanoyl chloride |
| c. resorcinol | g. 1-decanol |
| d. decanoic acid | h. anisole |

- | | |
|----------------------------------|---|
| i. sodium 1-naphthalenesulfonate | m. triethylammonium sulfate |
| j. 2-methylbutanamide | n. carbon monoxide |
| k. benzamide | o. <i>n</i> -butyltrimethylammonium bromide |
| l. succinimide | |

8. Six unlabeled bottles containing liquids were found on the organic reagent shelf. To aid in determining their contents, the bottles were labeled *A*, *B*, *C*, *D*, *E* and *F* and put to tests which gave the following results.

Water: *A* emulsified; the others were insoluble.

Br_2 in CCl_4 : *A* reacted rapidly and gave copious fumes. *D* and *F* slowly evolved HBr . *C* and *E* decolorized the reagent without forming fumes. *B* did not react.

Cold KMnO_4 : *B*, *D*, and *F* did not react. Color disappeared with *A*, *C*, and *E*.

Dilute NaOH : *A* dissolved; the others were insoluble.

Sodium: *A* and *D* evolved gas; *B* reacted rapidly, but gave no gas; *E*, and *F* did not react.

$\text{Ag}(\text{NH}_3)_2\text{OH}$: *C* gave a gray precipitate; the others did not react.

Conc. H_2SO_4 : Only *B* was insoluble.

Conc. HI : Upon heating, *C*, *D*, *E*, and *F* gave volatile oils which gave green flames on copper spirals. *A* and *B* did not change.

As a result of the tests, what conclusions can be drawn as to the nature of the liquids?

9. Arrange the compounds listed below in order of their acidities, beginning with the strongest acid. Use structural formulas.

<i>m</i> -cresol	1-butanol
butylamine	carbonic acid
butanoic acid	maleimide
phenylamine	

10. Arrange the compounds listed below in the order of their basicities, beginning with the strongest base. Use structural formulas.

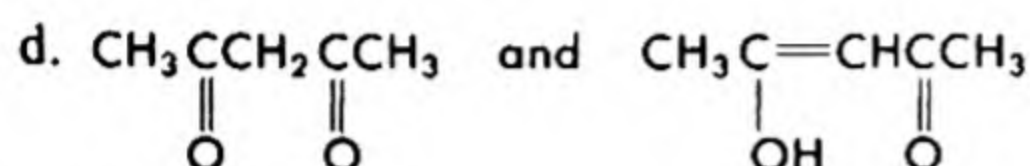
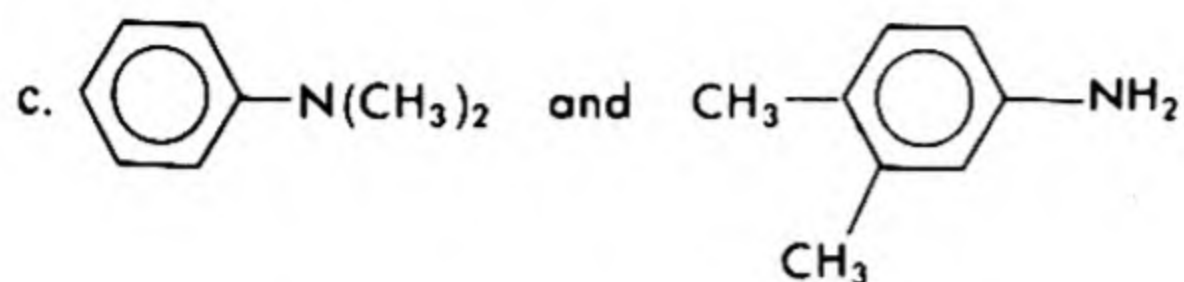
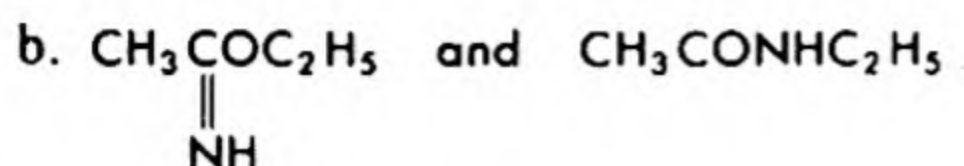
phenyl ether	isopropylamine
tetramethylammonium hydroxide	anisole
ethyl ether	<i>o</i> -toluidine

11. Show how the following pairs of compounds can be distinguished by simple chemical tests. State what observations would be the basis of the distinction.

- | | |
|---------------------------|--------------------------------|
| a. butane and 1-butene | e. butanone and methyl acetate |
| b. 2-butyne and 1-butyne | f. propanamide and benzylamine |
| c. phenol and 1-hexanol | g. acetamide and succinimide |
| d. propanal and propanone | |

12. Show how the following pairs of compounds can be distinguished by their infrared or ultraviolet spectra.

- a. $\text{CH}_3\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{COOH}$ and $\text{CH}_3\text{CHOHCOOH}$



13. Make the following identifications.

a. A compound which was either cetyl alcohol or α -naphthol was treated with alcoholic ferric chloride. A pale blue-violet color resulted. Which was it?

b. A volatile liquid which was either ethyl iodide or pentane reacted with magnesium in dry ether. Which was it?

c. A solid which was either benzophenone or phenyl ether gave a strong absorption peak at 5.7μ . Which was it?

14. Write equations for easily executed reactions in which both compounds in the following pairs of compounds show the *same positive observable results*. Use structural formulas and indicate conditions.

a. diisopropyl ether and 2-octene

b. benzoquinone and nitrobenzene

c. cyclopropane and propene

d. *p*-cresol and glutarimide

e. *m*-chlorophenol and acetylacetone

UNIT



Organic Reactions

10

Acidity and Basicity in Organic Compounds

10-1 DEFINITIONS OF ACIDS AND BASES

A. The Classical or Arrhenius Theory

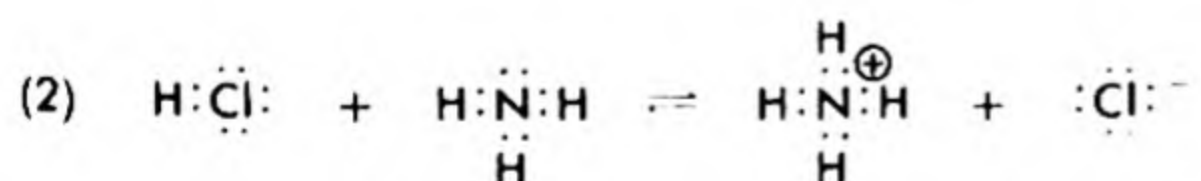
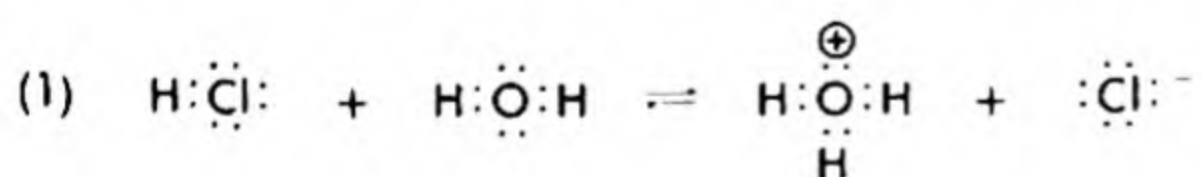
Early theories of ionization, most coherently expressed by Svante Arrhenius, defined an acid as a substance which furnishes hydrogen ions in water and a base as a substance which furnishes hydroxide ions in water.

The principal disadvantage of the Arrhenius treatment is the conceptual limitation of acids and bases to aqueous solutions. It is desirable to define acids and bases so as to treat similar phenomena in a similar manner regardless of solvent.

B. The Brønsted-Lowry Theory

J. N. Brønsted in Denmark and T. M. Lowry in England independently proposed just such a more general concept. An acid is a substance which can, under suitable conditions, donate a proton. A base is a substance which can accept a proton.

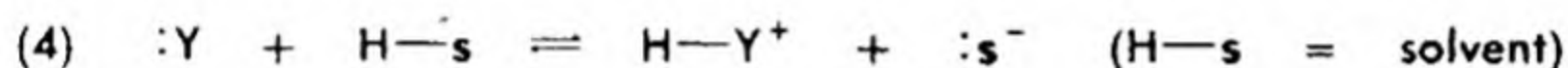
In accord with the generality of these definitions, it is seen that the reaction of hydrogen chloride with water (eq. 1) is analogous to the reaction of hydrogen chloride with ammonia (eq. 2).



The chloride ion produced in the reaction is called the *conjugate base* of hydrogen chloride; hydrogen chloride is the *conjugate acid* of the chloride ion. The hydronium ion is the conjugate acid of the water molecule; the ammonium ion is the conjugate acid of the ammonia molecule. Members of a conjugate pair are related to each other by gain or loss of one proton.

The Brønsted-Lowry concept is an operational one since substances are acids or bases as they donate or accept protons in a given reaction. However, it is apparent that some substances have more tendency to donate protons than others, that is, are stronger acids, and that some substances have more tendency to accept protons than others, that is, are stronger bases.

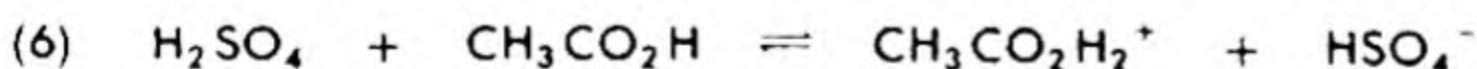
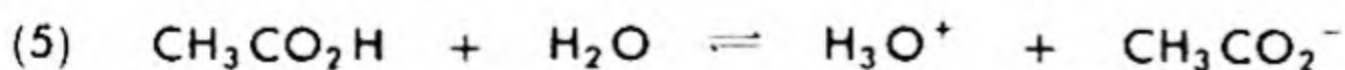
Conceivably, an acidity scale and a basicity scale could be constructed which would express acid strengths and base strengths in terms of the relative proton-donating or proton-accepting abilities of the compounds. In a limited way, acidity can be described in terms of the strength of a substance as an electrolyte in a particular basic solvent, the equilibrium constant of eq. (3). Similarly, basicity can be described in terms of the strength of a substance as an electrolyte in a particular acidic solvent, the equilibrium constant of eq. (4). Unfortunately, this method is limiting,



not general, because any real solvent has a certain level at which its own electrolytic strength is effective in leveling out the ionization of very strong or very weak acids or bases. For example, all acids stronger than acetic acid are completely ionized in liquid ammonia; conversely, all bases stronger than ammonia are completely ionized in glacial acetic acid. On the other hand, acids weaker than ammonia fail to ionize in ammonia appreciably more than ammonia itself, and bases weaker than acetic acid fail to ionize in acetic acid appreciably more than the solvent.

Nevertheless, acidity and basicity are intrinsic properties of substances, in the same way that ionization potentials are intrinsic properties of elements; but acid strengths and base strengths are solvent-related in the same way that electrode potentials show solvent effects.

Certain substances may act as either acids or bases, depending on circumstances. Such substances are designated *amphoteric* or *ambiprotic*. For example, water is the conjugate base of the acid hydronium ion (eq. 1) and is the conjugate acid of hydroxide ion. Similarly, acetic acid acts as an acid in water (eq. 5), its ionization (proton transfer to water) being only moderate, whereas it acts as a base in concentrated sulfuric acid (eq. 6) where the proton transfer is essentially complete.

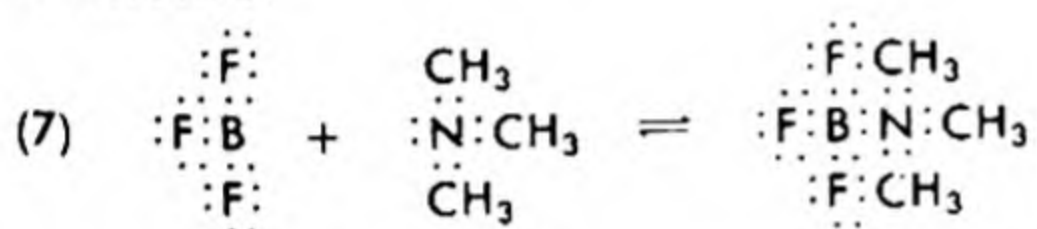


We shall make much use of the Brønsted-Lowry concept in organic chemistry since proton transfers are of key importance to many organic (as well as inorganic) reactions.

C. The Lewis Theory

The Brønsted-Lowry treatment of acids and bases discards the notion that hydroxide ions are involved in all reactions of bases and instead focuses attention on the idea that bases donate electron pairs by sharing them with the protons donated by acids. Some chemists consider that this is still too restrictive, as the proton is made a special case when it is only one of many electron-deficient species which can undergo an analogous reaction (i.e., the coordination of an electron pair into the valence shell of one of the atoms of an electron-accepting molecule or ion).

Gilbert N. Lewis, one of the most prominent physical chemists of the early twentieth century, was foremost among those who defined acids and bases so as to equate all electron-pair acceptors. Thus, an acid may be defined as a substance which accepts electron pairs; a base, a substance which has available electron pairs. The reaction between boron trifluoride and trimethylamine is considered to parallel that between a proton and ammonia.



The Lewis theory serves the valuable function of relating seemingly diverse chemical phenomena and showing them to be fundamentally alike in cause and result. This theory is often applied as a generalized theory of reactions in which proton acid-base reactions form a special case. Most organic chemists find both the Brønsted-Lowry concept and the Lewis concept separately useful. It should be apparent that a Lewis base is also a Brønsted base. However, such electron-deficient species as boron trifluoride (eq. 7), aluminum chloride, AlCl_3 , and zinc chloride, ZnCl_2 , are called Lewis acids to distinguish them from proton-donating or Brønsted acids.

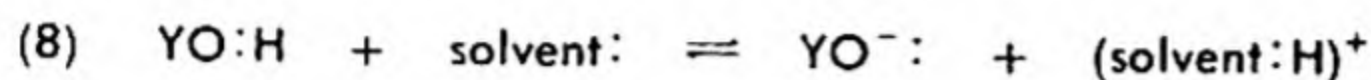
10-2 ACIDITY AND ORGANIC ACIDS

All compounds which contain hydrogen can be considered acids in the Brønsted sense, since, potentially, they can become proton donors. Significant acidity, however, is found only in compounds in which hydrogen atoms are present on atoms of elements of the fifth, sixth, and seventh groups of the periodic table, or on carbon atoms especially activated by adjacent functional groups. However, under appropriate conditions even hydrocarbons may function in acid-base reactions.

A. Molecular Factors Producing and Modifying Acidity

The strength of an acid depends upon its relative ability to donate a proton, and, conversely, upon the reluctance of its conjugate base to

accept a proton. Thus, stronger acids are conjugate to weaker bases, and weaker acids are conjugate to stronger bases. An introductory discussion of the effects of electron distribution upon the strengths of acids is given in §7-3A(2), and it is suggested that the student review this material at this time. In summary, it is to be recalled that in the equilibrium (8), electrical



or other effects that stabilize YO^- more than they do YOH make the acid YOH stronger, while those that stabilize YOH more than YO^- make YOH a weaker acid.

Any effect in a molecule which operates to withdraw electrons from the atom bound to hydrogen, or increase stability of the conjugate base, tends to increase acid strength. Any effect which operates to release electrons toward the hydrogen atom, or decrease stability of the conjugate base, tends to hinder acidic ionization.

Acid strength increases as hydrogen is attached to an atom of higher atomic number in a period; acid strength of $\text{HF} > \text{HOR} > \text{HNR}_2 > \text{HCR}_3$, in which R is hydrogen or comparable hydrocarbon groups.

Acid strength also increases as hydrogen is directly attached to an atom of higher atomic number in a group; acid strength of $\text{ROH} < \text{RSH} < \text{RSeH}$, in which R is hydrogen or an alkyl group.

Consideration of the relative strengths of organic acids has been of prime importance to the general understanding of theoretical organic chemistry, and it is therefore worthwhile to scrutinize certain data closely. Table 10-1 lists the ionization constants of certain substituted acetic acids in order of increasing acid strength. We see that, compared to hydrogen, alkyl groups lower the acid strength whereas electron-attracting atoms or groups such as halogen atoms increase acid strength. These data have led to a concept called the *inductive effect*, which represents a mode of transfer of electrical charge within a molecule and which results from the dipolar

TABLE 10-1. Ionization Constants for the Dissociation of Certain Substituted Acetic Acids in Water at 25°

Acid	$10^5 K_a$	Acid	$10^5 K_a$
$\text{CH}_3\text{—CH}_2\text{COOH}$	1.3	$\text{Br—CH}_2\text{COOH}$	138
$\text{H—CH}_2\text{COOH}$	1.8	$\text{Cl—CH}_2\text{COOH}$	155
$\text{C}_6\text{H}_5\text{—CH}_2\text{COOH}$	5.6	$\text{F—CH}_2\text{COOH}$	217
$\text{CH}_3\text{O—CH}_2\text{COOH}$	33.	Cl_2CHCOOH	5140
$\text{I—CH}_2\text{COOH}$	75.	Cl_3CCOOH	121,000

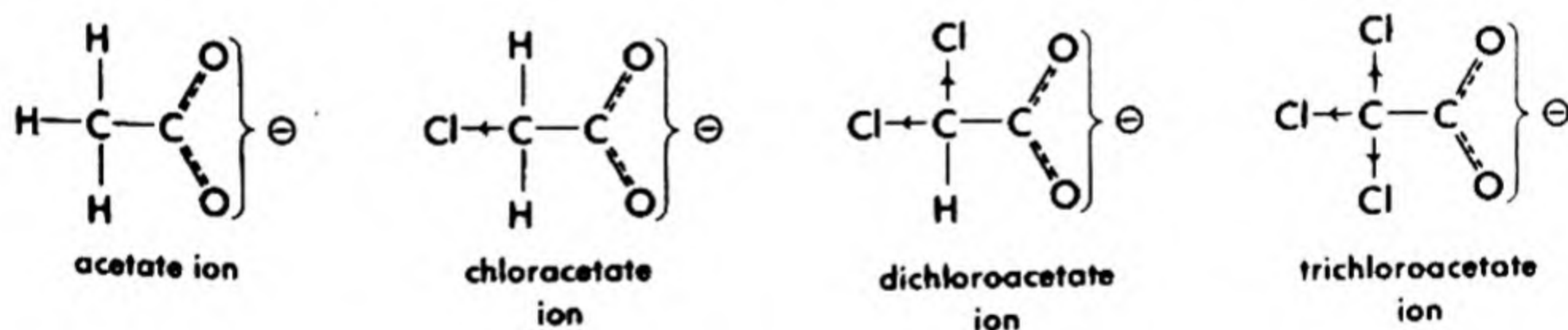
character of bonds between atoms of different elements or between atoms of the same element in different bonding environments.

B. Permanent Inductive Polarization in Molecules

Polarity in molecules is a consequence of the differing electron attractions of their constituent atoms. In saturated molecules the polarization is assumed to be carried down the chain by electrical induction. A chlorine atom induces a positive charge in the adjacent carbon atom, which in turn induces electrons to move toward it from adjacent carbon and hydrogen atoms, making them positive, and so on down the chain. Such polarization is called an *inductive effect*.

C. Inductive Effects as Measured by Acid Strengths

It should be clear that when dipoles are set up as described in the previous section, these have effects of importance in stabilizing acids or their conjugate bases. We may choose hydrogen as our standard, compared to which alkyl groups are shown to be electron donating, whereas aryl, methoxy, and halogens are manifestly electron attracting. Indeed, we can set up a series of relative electron-attracting or electron-donating properties for atoms or groups based upon acid-strength data. Because the induced polarizations set up by bond dipoles are roughly additive, dichloroacetic acid is stronger than chloroacetic acid and trichloroacetic is still stronger, each chlorine atom contributing to a bond dipole of such a nature as to stabilize the anionic charge on the conjugate base.

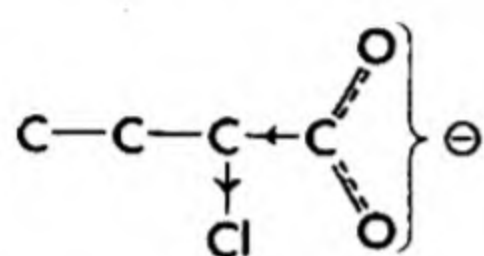
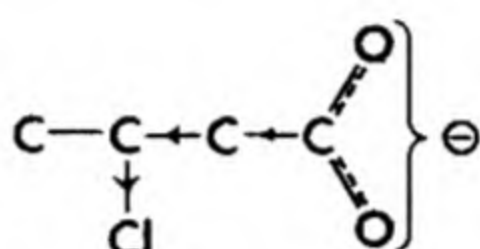
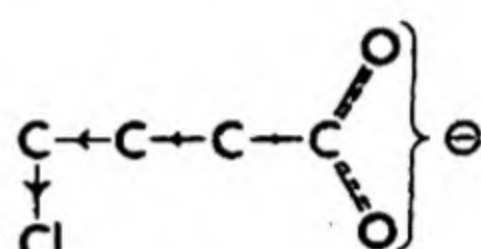


The nature of the inductive effect is such that each bond dipole is screened in part by the electron clouds of the atoms on which it operates, so that each of the induced dipoles in sequence along a saturated chain of atoms away from the original dipole is considerably smaller than the preceding dipole. An important result of this is that the inductive effect of an atom or group is greatest when the polarizing group is close to the position where the effect is measured and becomes progressively less important as the distance between groups and effect is increased. This is demonstrated clearly in the monochloro substituted *n*-butyric acids (Table 10-2), in which an *alpha*-chloro substituent increases the acid strength to 100 times that of the unsubstituted acid, while this increase is lowered to a

TABLE 10-2. Ionization Constants for the Dissociation of Chlorinated *n*-Butyric Acids in Water at 25°

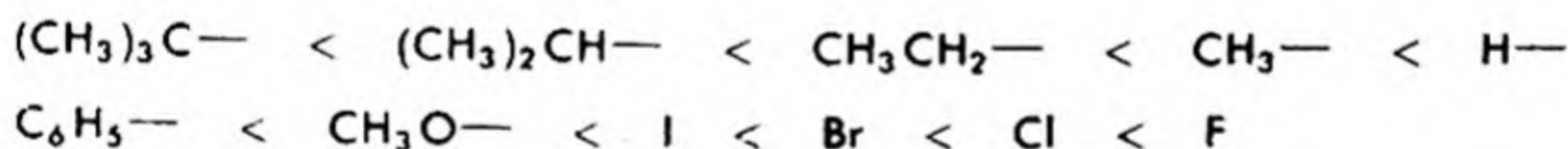
Acid	$10^5 K_a$
$\text{CH}_3\text{—CH}_2\text{—CHCl—COOH}$	140
$\text{CH}_3\text{—CHCl—CH}_2\text{—COOH}$	8.8
$\text{CH}_2\text{Cl—CH}_2\text{—CH}_2\text{—COOH}$	3.0
$\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$	1.5

factor of only two when the chlorine is in the gamma position (see formulas below).

 α -chloro β -chloro γ -chloro

The electron-donating properties of alkyl groups can be emphasized by comparing the acid strengths of formic acid H—COOH and acetic acid $\text{CH}_3\text{—COOH}$; formic acid is about ten times as strong as acetic acid.

From data such as these it is possible to develop an order of inductive release or withdrawal of electrons. A partial list in order of increasing electron attraction is as follows:

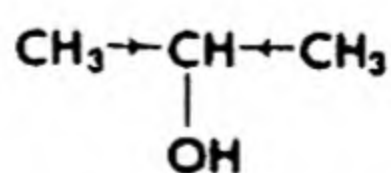


We shall see that this order has general applicability in organic chemistry.

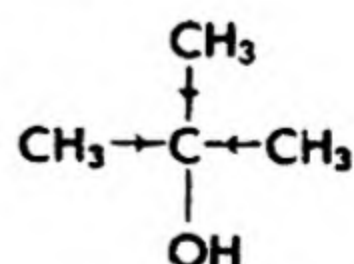
The inductive effect is also responsible for differing acidities in different types of alcohols, as observed in the rates of their reactions with active metals and in the base strengths of the conjugate alkoxide ions. Alkyl groups are more electropositive than hydrogen atoms. Thus, a larger number of hydrogen atoms on the carbinol carbon atom tends toward greater stability of alkoxide ions and greater acidity of alcohols. The order of acidity is 1° alcohol $>$ 2° alcohol $>$ 3° alcohol, and this is also the order of reactivity with active metals. Thus, methanol and primary alcohols react vigorously with sodium, secondary alcohols less vigorously, and tertiary alcohols such as 3° -butyl alcohol very sluggishly.



ethanol

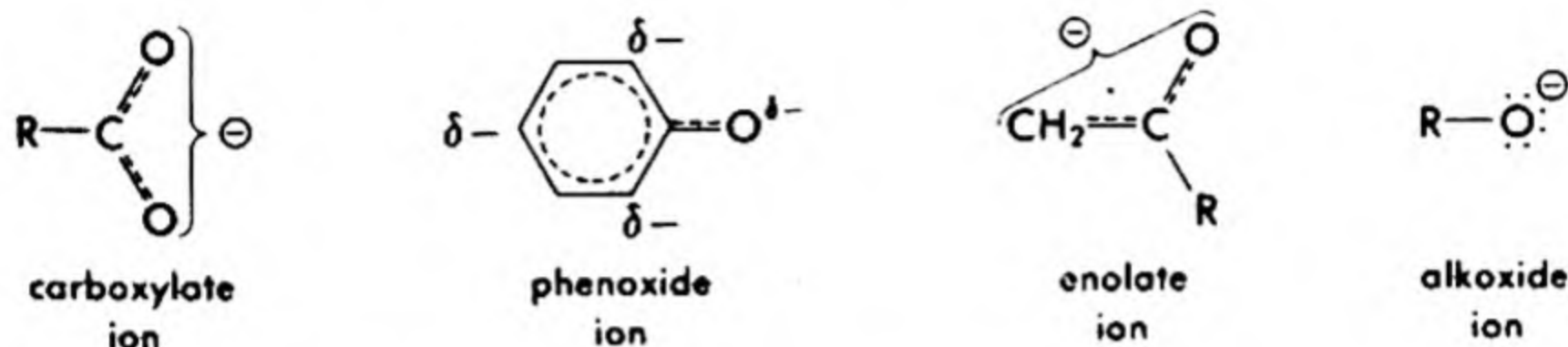


isopropyl alcohol

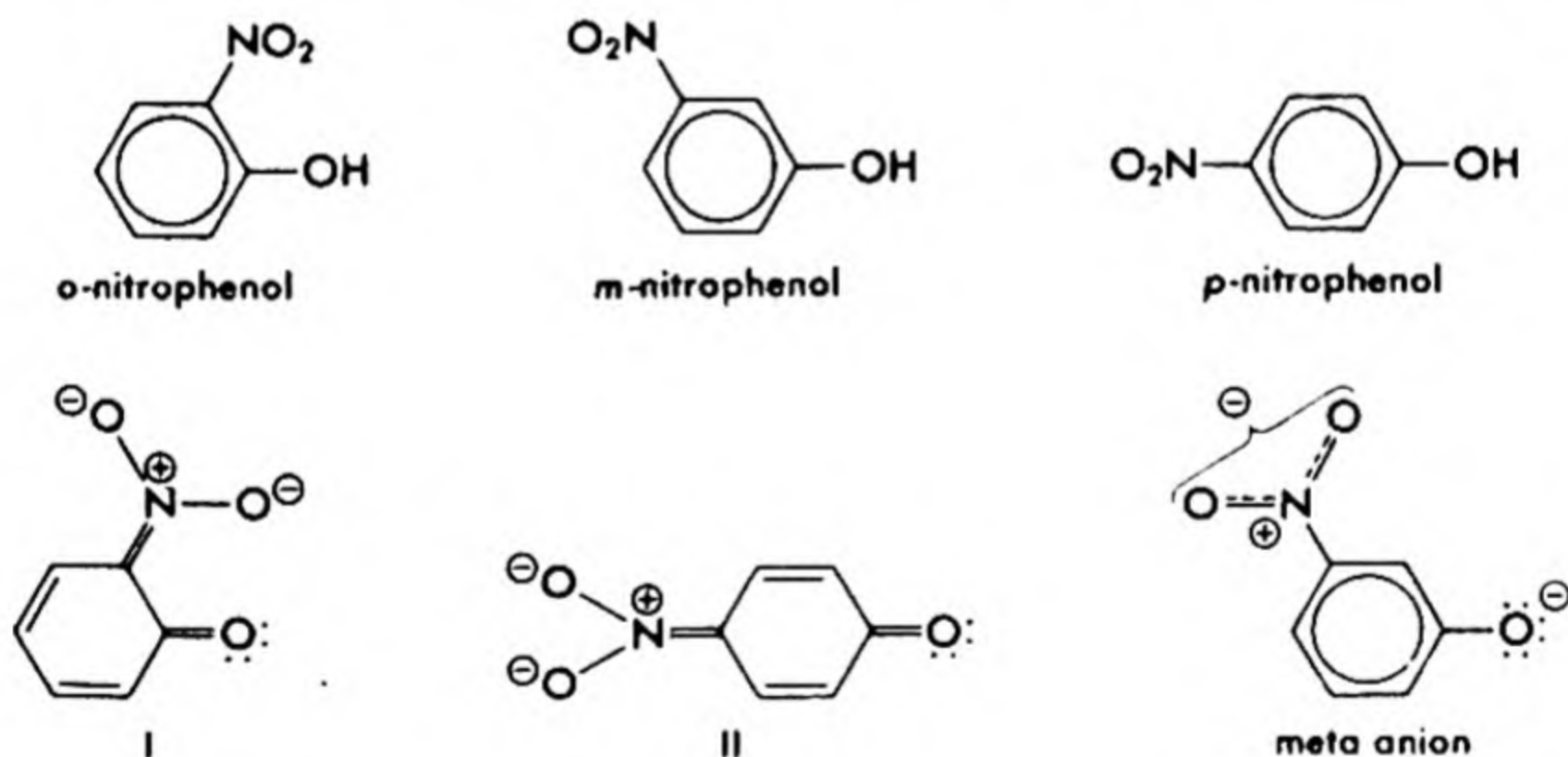
 3° -butyl alcohol

D. Conjugative Effects in Modifying Acid Strengths

Even more pronounced in its effects on acidity is conjugative electron withdrawal of the electron pair released in the formation of the conjugate base of an acid. This process has been discussed at length in §7-3A(2) and was shown to be responsible for a substantial portion of the large increase in acid strength of carboxylic acids as compared with alcohols. The electron delocalizations in carboxylate anions, phenoxide ion, and enolate ions are shown as compared with alkoxide ions.

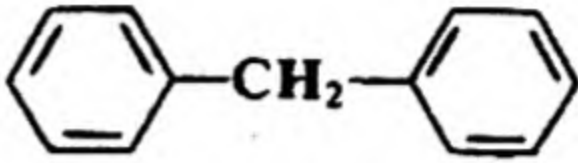


The effects of extended conjugation can be observed in the acid strengths of *ortho*-, *meta*-, and *para*-nitro-substituted phenols. Inspection of these systems show that only the *ortho*- and *para*-substituted phenoxides are conjugated (the appropriate valence bond structures, I and II, are shown), while in the *meta* anion, the nitro group has no conjugative relationship with the electrons on the oxygen of the anion. On the basis of



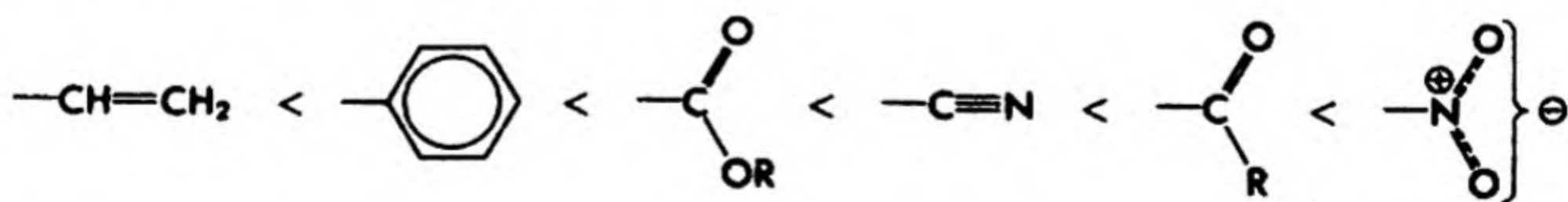
our experience with inductive effects (and the knowledge that the nitro group is electron withdrawing compared with hydrogen), we would predict (in the absence of conjugative effects) that the order of acidity would be *ortho* > *meta* > *para*. In fact, however, *para* and *ortho* nitrophenol have ionization constants of 6.9 and 6.2×10^{-8} respectively; the *meta* value is 1×10^{-8} and phenol itself is 1×10^{-10} . Here, then, we again have evidence regarding the special stabilizing effects of electron-delocalization on the conjugate base anion. Again the effects are roughly addi-

TABLE 10-3. Approximate Dissociation Constants for Some Acids Involving ionization of a Carbon-Hydrogen Bond

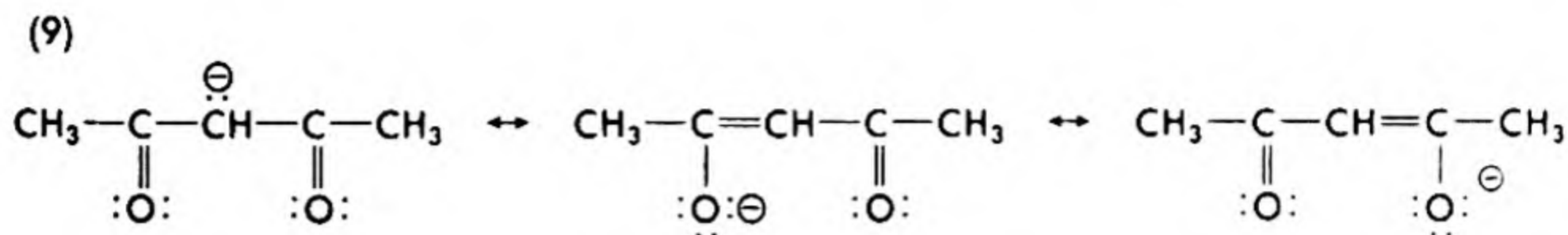
Name	Formula	K_a
Ethane	CH_3CH_3	$\approx 10^{-41}$
Diphenylmethane		$\approx 10^{-35}$
Acetone	$\text{CH}_3\text{C}(=\text{O})\text{CH}_3$	$\approx 10^{-20}$
bis-Methylsulfonylmethane	$\text{CH}_3\text{SO}_2\text{CH}_2\text{SO}_2\text{CH}_3$	1×10^{-14}
Ethyl malonate	$\text{C}_2\text{H}_5\text{OC}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{OC}_2\text{H}_5$	5×10^{-14}
Malononitrile	$\text{N}\equiv\text{CCH}_2\text{C}\equiv\text{N}$	6×10^{-12}
Ethyl acetoacetate	$\text{CH}_3\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{OC}_2\text{H}_5$	2×10^{-11}
Acetylacetone	$\text{CH}_3\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{CH}_3$	1×10^{-9}
Nitromethane	CH_3NO_2	6×10^{-11}
Dinitromethane	$\text{O}_2\text{NCH}_2\text{NO}_2$	3×10^{-4}

tive, 2,4-dinitrophenol having an ionization constant of 1×10^{-4} and picric acid (2,4,6-trinitrophenol) about 4×10^{-1} .

Groups that are capable of electron withdrawal by the conjugative effect are of the general type $-\text{A}=\text{B}$ and function best when B is more electron attracting than A (assuming that A is the atom bonded to the system donating the electrons). An *approximate* order of *conjugative electron withdrawal* is as follows:



The effects of such groups in stabilizing anions may be seen from the data in Table 10-3 showing cases in which protons are removed from carbon atoms in the acid-base equilibrium. For example, stabilization of the acetylacetone conjugate anion involves the canonical structures in eq. (9).



E. Acid Strengths of Benzoic Acids: Coexistence of Conjugative and Inductive Effects

In comparing strengths of aromatic acids with those of aliphatic acids, we note that the phenyl group (like the methoxyl and other groups) shows opposing inductive and conjugative effects. When the phenyl group is insulated from the carbonyl group, as in phenylacetic acid, its large inductive electron withdrawal stabilizes the phenylacetate ion in respect to the phenylacetic acid molecule (Fig. 10-1). However, benzoic acid shows an anomalously *low* acid constant compared with formic acid (Fig. 10-2). While the inductive effect of the phenyl group still tends to stabilize the benzoate ion, the conjugative effect of the phenyl group causes a more than compensating stabilization of the benzoic acid molecule, which has the overall effect of *decreasing* the acidity of benzoic acid compared with formic acid.

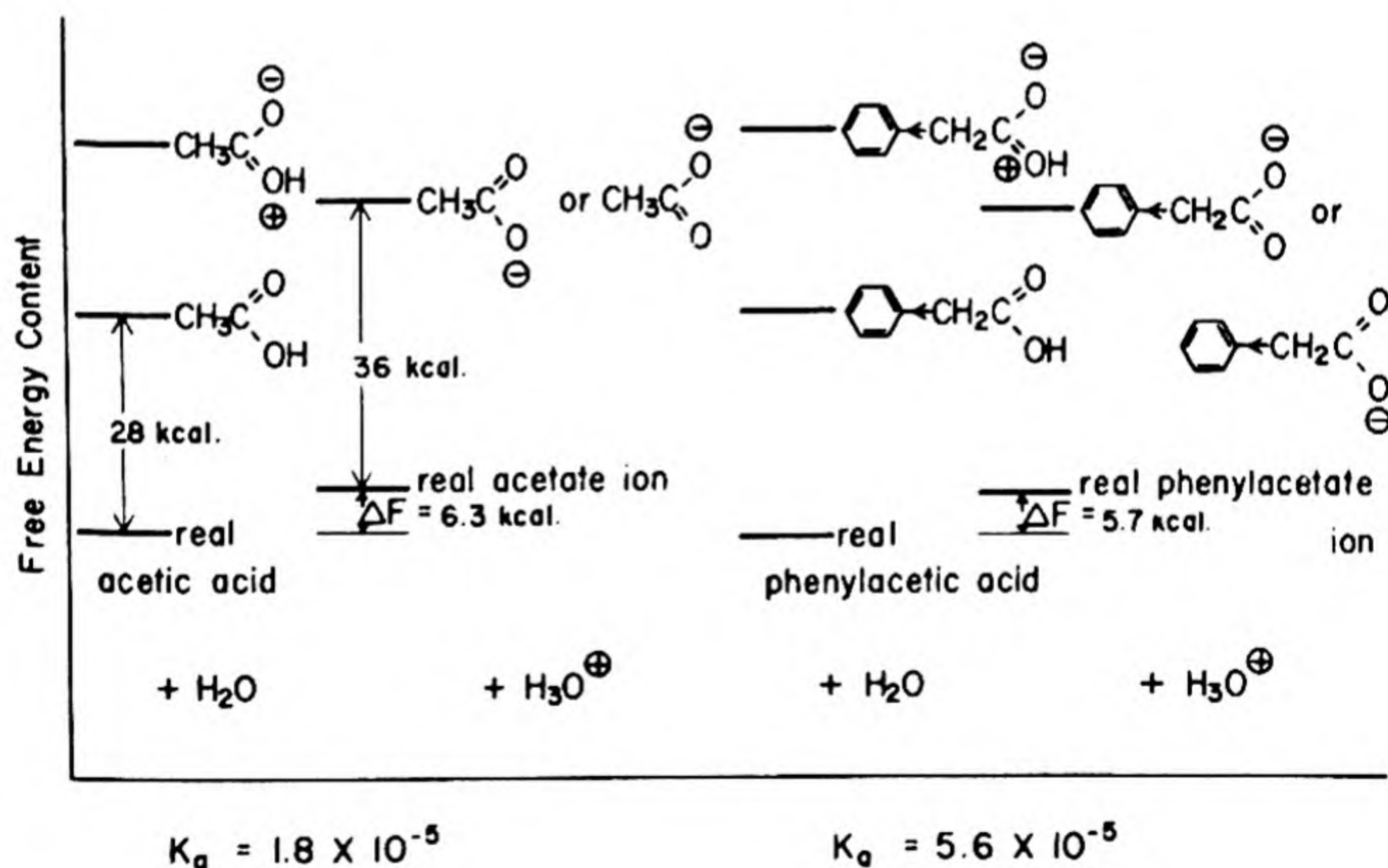


Fig. 10-1. Energy Diagrams Which Show Inductive Effect of Benzene Ring as Stabilizing Phenylacetate Ion More than Phenylacetic Acid. Benzene ring is "insulated" from carboxyl group by CH_2 ; hence, no resonance effect.

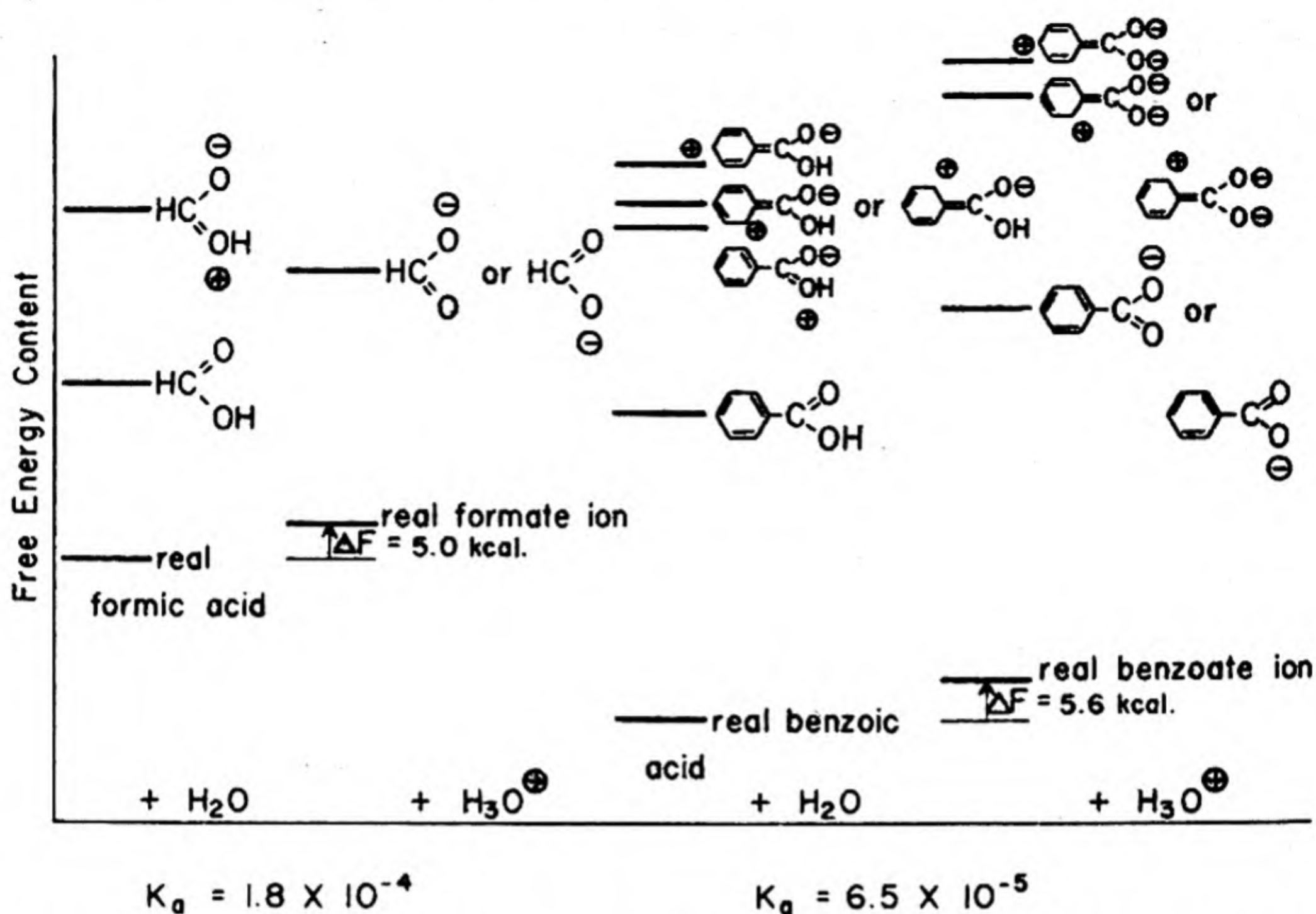
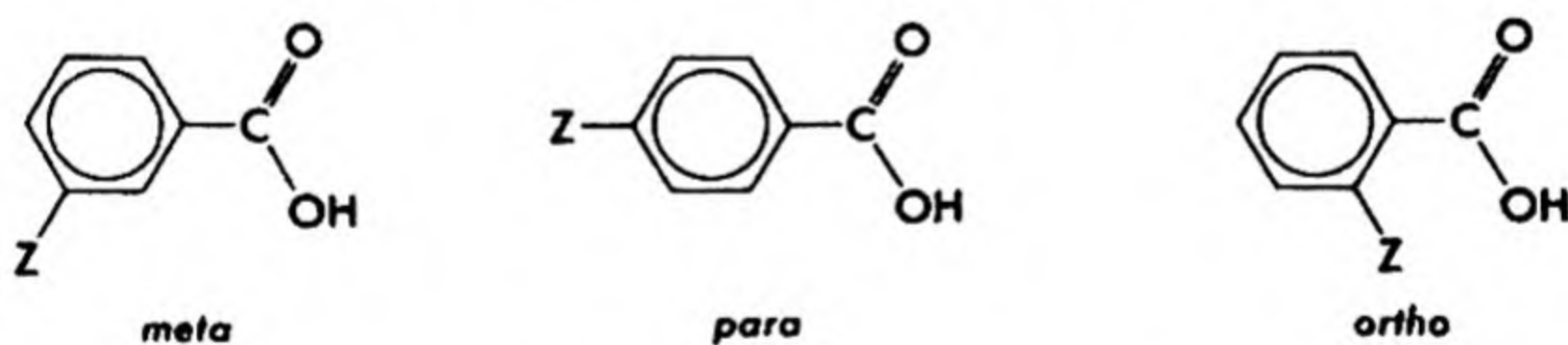


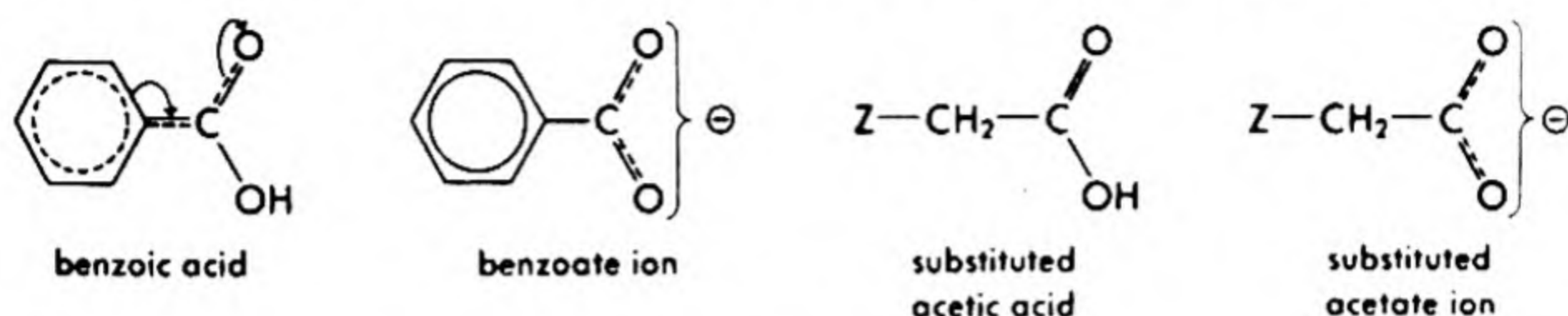
Fig. 10-2. Energy Diagrams Which Show Resonance Effects of Benzene Ring as Stabilizing Benzoic Acid More than Benzoate Anion.

The dissociation constants of certain monosubstituted benzoic acids are given in Table 10-4. At first we will consider only the *meta*- and *para*-substituted acids, since the *ortho*-substituted acids have special steric

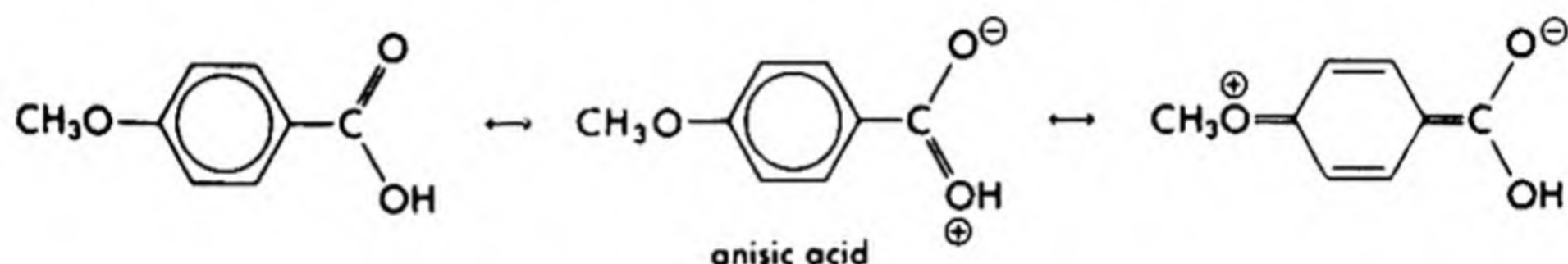


(spatial) problems and must therefore be discussed separately. In the *para*-substituted acid a number of anomalies becomes apparent immediately in the order of acidities. We note that methyl is an electron-releasing group compared with hydrogen, as it is in the substituted acetic acid, but that the methoxy group is apparently electron releasing in the *para* position and electron withdrawing (as expected) in the *meta* position. The principal parts of the explanation are fundamental to several related organic chemical phenomena of considerable importance. In benzoic acid and in its corresponding anion, the benzene ring is directly attached to the carboxyl or carboxylate group and is therefore conjugated with it.

This is quite different from the situation in substituted acetic acids and their conjugate anions, where the methylene group acts as an insulator so that conjugation between Z and the carboxyl group is not possible.



Thus, groups that are electron releasing by a conjugative effect (i.e., have polarizable p or π electrons to donate) when appropriately placed on the aromatic ring tend to stabilize the acid form more than the conjugate base, where the carbonyl group is already totally involved with the anionic oxygen. Such an effect of methoxyl, shown in the valence-bond structures for anisic acid, is responsible for the acid-weakening effect of

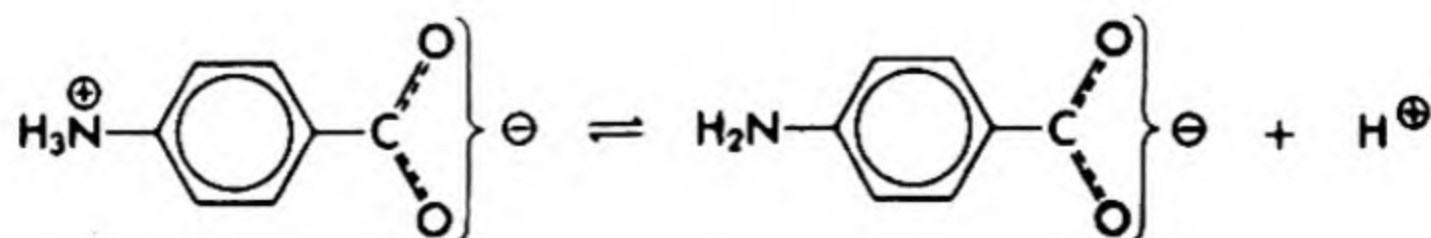


methoxyl or hydroxyl when substituted in the *para* position. With methoxyl in the *meta* position, or substituted on an acetic acid molecule, conjugation is not possible, so that only the electron-withdrawing effect of the methoxyl group is observed.

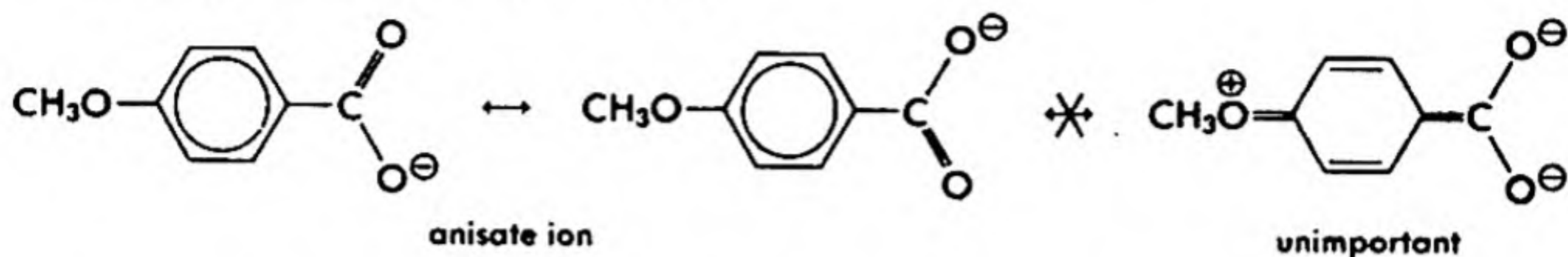
TABLE 10-4. Acid Dissociation Constants for Monosubstituted Benzoic Acids

	<i>para</i> substituents $10^5 K_a$	<i>meta</i> substituents $10^5 K_a$	<i>ortho</i> substituents $10^5 K_a$
$-\text{NH}_2$	1.2 ^a	1.5 ^a	—
$-\text{CH}_3$	4.5	5.2	13.0
$-\text{H}$	6.8	6.8	6.8
$-\text{OCH}_3$	3.3	8.2	8.2
$-\text{Cl}$	11	15	130
$-\text{NO}_2$	40	35	620

^a Acidities of ammonio acids are most often those of the ammonio group, $-\text{NH}_3^+$.



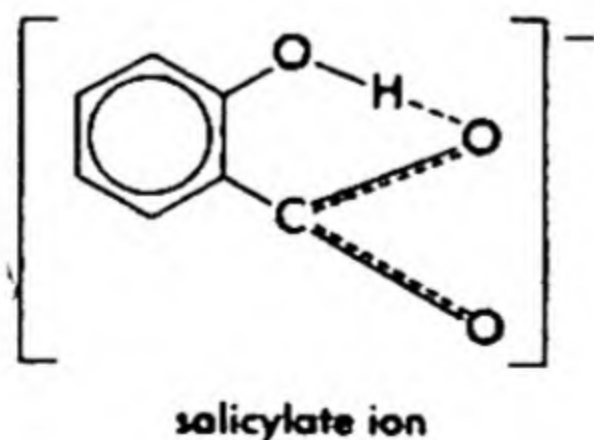
The delocalization of positive charge contributes considerable stability to anisic acid. On the other hand, comparable resonance in anisate ion is of less importance, since charge separation is in the direction to force like charges into close proximity.



Among the groups that exhibit electron release by conjugative effects (i.e., have polarizable p or π electrons) are $\text{CH}_2=\text{CH}_2-$, , $\text{R}_2\ddot{\text{N}}-$, $\text{R}\ddot{\text{N}}\text{H}-$, $\text{H}_2\ddot{\text{N}}-$, $\text{H}\ddot{\text{O}}-$, $\text{R}\ddot{\text{O}}-$, $:\ddot{\text{I}}-$, $:\ddot{\text{Br}}-$, $:\ddot{\text{Cl}}-$, and $:\ddot{\text{F}}-$. Certain groups (e.g., phenyl and vinyl) may either accept or donate electrons by conjugation. Also, as noted above, certain groups have electron-withdrawing tendencies by induction, but in certain situations, may release electrons by conjugation. The latter groups include amino, hydroxyl, alkoxyl, and halogen functions.

Groups *ortho* to the carboxyl function are so close that they influence acidity by forces operating directly across space. They appear to operate in many cases by twisting the carboxyl group out of the plane of the benzene ring. This reduces the conjugation between the ring and the carbonyl group (as π - π overlap with consequent electron delocalization requires that these orbitals lie in the same plane). As noted, this conjugation with consequent stabilization is more important in the acid than in the anion; for this reason its loss destabilizes the acid more than the anion and makes the acid stronger.

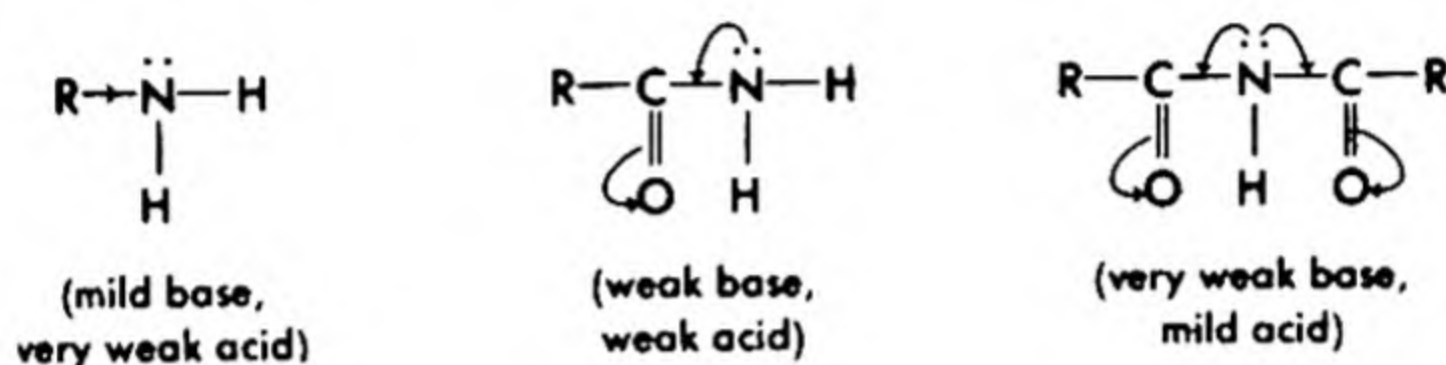
Intramolecular hydrogen bonding in the salicylate ion stabilizes that ion very substantially with respect to the acid, so that salicylic acid is about 35 times as strong as *p*-hydroxybenzoic acid. This stabilization results



from distribution of the negative charge over *three* (instead of two) oxygen atoms, as well as the various positions in the ring conjugated with these.

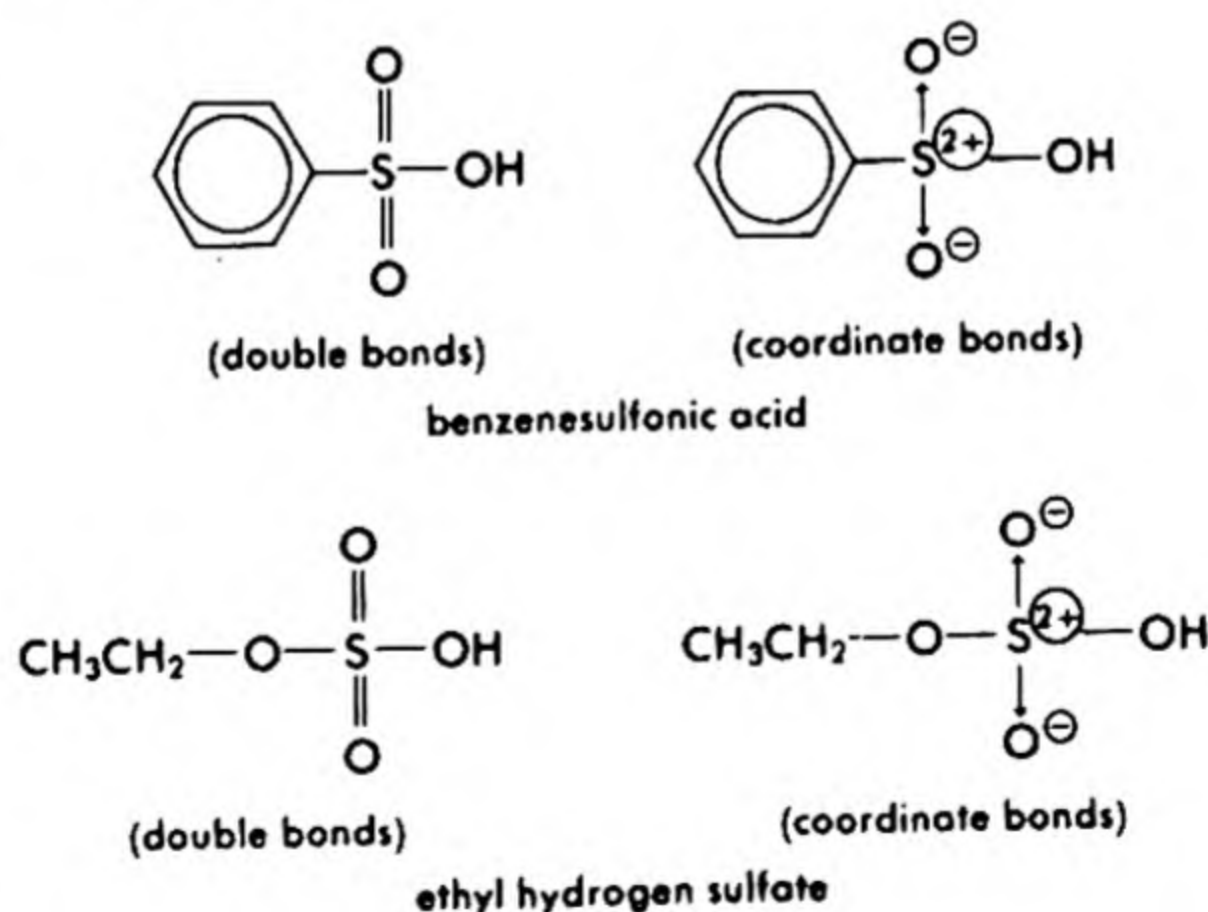
F. Acidity in Miscellaneous Groups

Groups attached to the nitrogen atom have effects similar to those of the same groups attached to an oxygen atom. Hence, aliphatic amines are the least acidic of the ammonia derivatives. Aromatic amines are about as much more acidic than aliphatic amines as phenols are than alcohols. Increase in acidity of amides over aliphatic amines corresponds to increase in acidity of carboxylic acids over alcohols. The presence of two acyl groups on a nitrogen atom still further enhances acidity of hydrogen on the nitrogen. An imide is comparable to a phenol in acidity.



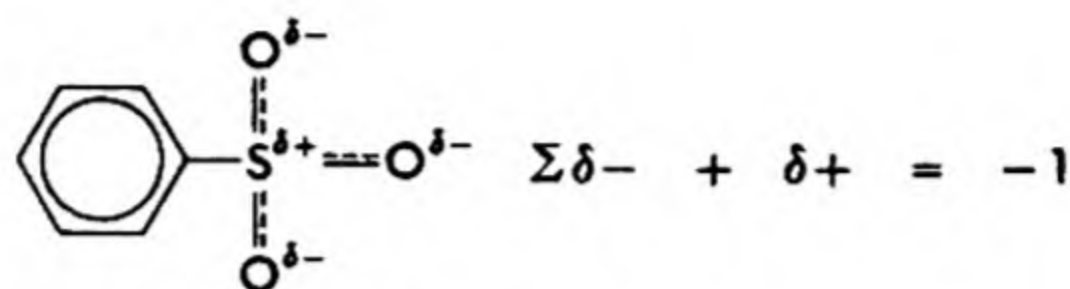
G. Sulfonic Acids and Alkyl Acid Sulfates

The explanation of the high acid strengths of sulfonic acids and of alkyl acid sulfates (as well as that of sulfuric acid) perhaps needs separate discussion. Chemists have vacillated between multiply bonded structures and coordinate covalent structures for the sulfur-oxygen bonds in these compounds and their derivatives. The most recent data appear to favor a resonance hybrid between these structures, but very much closer to the coordinate covalent structure.



If resonance is important in these compounds, it must be more important in the conjugate anions, which have three equivalent oxygen

atoms and involve charge delocalization, than in the acids, which have only two equivalent oxygen atoms and involve charge separation. Of considerable importance is the positive charge on the sulfur atom (probably somewhat less than the formal 2+), which greatly stabilizes the negative charge in the anion.



possible resonance hybrid
for benzenesulfonate ion

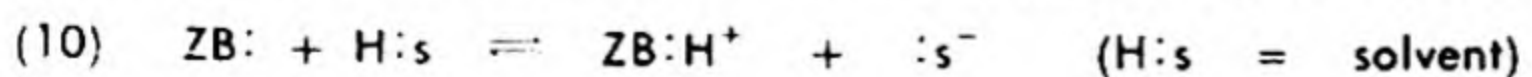
10-3 BASICITY AND BASIC ORGANIC COMPOUNDS

All organic compounds which have unshared electron pairs, or can acquire unshared electron pairs through appropriate electronic shifts, can be considered to be Brønsted or Lewis bases. Relatively strong bases form salts (which usually dissolve) with aqueous hydrochloric acid. Somewhat weaker bases form hydrochlorides with dry hydrogen chloride, while still weaker bases form salts with concentrated sulfuric acid.

The most important class of organic compounds having nonbasic unshared electrons toward sulfuric acid is that of the alkyl and aryl halides. They do, however, often coordinate with strong Lewis acids, such as aluminum chloride, and are weakly protonated by strong Brønsted acids.

A. Molecular Factors Producing and Modifying Basicity

The strength of a base depends on the ease of acceptance of a proton onto an unshared pair of electrons, or conversely, the firmness with which the proton is held, once captured, on the conjugate acid. To recapitulate, strong bases are conjugate to weak acids and weak bases to strong acids. It should be clear from the preceding discussion regarding acid strengths and from the Brønsted theory relating acids and bases, that the factors affecting base strength are analogous to those affecting acid strength. Basicity is increased when, in the equilibrium (10), electrical or other effects stabilize ZBH^+ more than they do ZB , and base strength is decreased when they stabilize ZB more than they do the conjugate acid.



Because of the relative kernel charges, the order of basicity of compounds of second period elements is $\text{R}_3\text{N:} > \text{R}_2\ddot{\text{O}} > \text{R}\ddot{\text{F}}:$. For negative

ions, the same order of basicity applies, $R_3C:^- > R_2N:^- > RO:^- > :\ddot{F}:^-$. The basic strengths of the anions are considerably greater than those of the related conjugate acids because of the negative charges. (In the case of R_3CH the lack of basicity is due to the lack of an available electron pair in the hydrocarbon.)

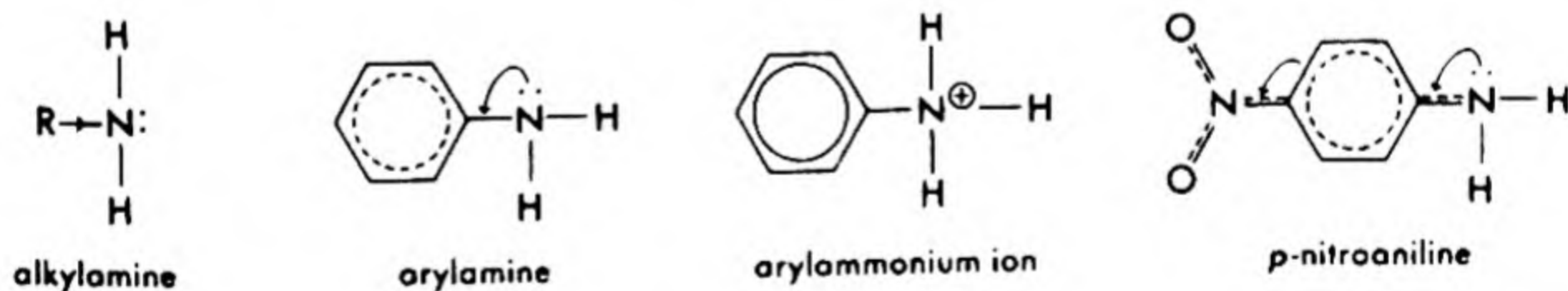
In a group of the periodic table, the basicity of elements in neutral compounds decreases down the group. Thus, $R-\ddot{S}-R$ is less basic than $R-\ddot{O}-R$ and $:\ddot{O}H^-$ is a stronger base than $:\ddot{S}H^-$.

B. Comparison of Basicity in Organic Compounds

The relative base strengths of several compounds are given in Table 10-5. The base constant given in the graph is the equilibrium constant: $K_b = [HB^+]/[H^+][B]$. This is the inverse of the acid ionization constant of the conjugate acid.


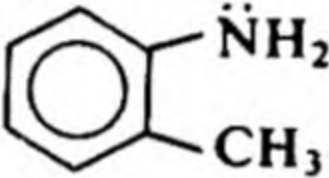

The most common organic bases are the amines. Basicity in these compounds is due to unshared electrons on the nitrogen atom. Since alkyl groups are electron releasing; alkyl and dialkyl amines are somewhat more basic than ammonia.

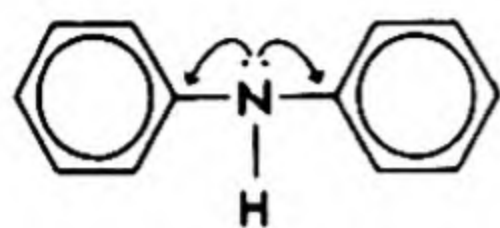
Aryl groups, which increase acidity of hydroxy groups due to the effects of resonance interaction with the ring, decrease basicity of amino groups by the same means; thus arylamines are more highly stabilized by resonance than arylammonium ions. As might be anticipated, *p*-nitroaniline is much less basic than aniline, as the conjugation energy lost in formation of the *p*-nitroanilinium ion is greater than that lost with the unsubstituted base. Because diphenylamine and triphenylamine have corresponding greater resonance energy to lose in forming protonated species, they are progressively weaker bases. Diphenylamine is insoluble in dilute hydrochloric acid, but dissolves in concentrated sulfuric acid (see eq. 11). This reagent does not dissolve triphenylamine.



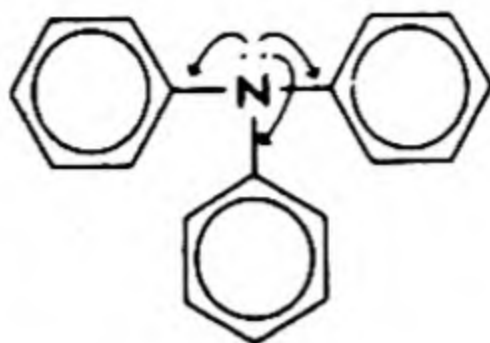
Acyl groups, which enhance acidity in hydroxy and other groups markedly, correspondingly decrease basicity of amino groups. Simple amides are little more basic than water.

TABLE 10-5. Strengths of Various Bases at 20–25°

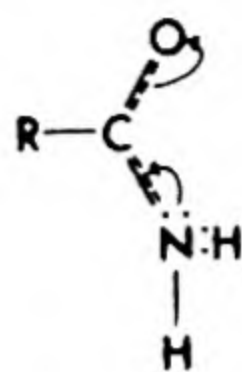
Name	Formula	Approximate $K_b = \frac{[HB^+]}{[H^+][B]}$
Guanidine	$(H_2N)_2C=\ddot{N}H$	(water reference) 2×10^{13}
Acetamidine	$CH_3-C \begin{array}{l} \nearrow \ddot{N}H \\ \searrow NH_2 \end{array}$	3×10^{12}
Dimethylamine	$(CH_3)_2\ddot{N}H$	5×10^{10}
Methylamine	$CH_3\ddot{N}H_2$	4×10^{10}
Trimethylamine	$(CH_3)_3N:$	5×10^9
Ammonia	$H_3N:$	2×10^9
Pyridine		2×10^5
<i>p</i> -Toluidine	$CH_3-\text{C}_6\text{H}_4-\ddot{N}H_2$	1×10^5
Aniline	$C_6H_5\ddot{N}H_2$	4×10^4
<i>o</i> -Toluidine		2×10^4
Urea	$(H_2N)_2C=O:$	2×10^1
<i>p</i> -Nitroaniline	$O_2N-\text{C}_6\text{H}_4-\ddot{N}H_2$	1×10^1
Diphenylamine	$(C_6H_5)_2\ddot{N}H$	8×10^0
Pyrrole		5×10^{-1}
Acetamide	$CH_3C \begin{array}{l} \nearrow O: \\ \searrow NH_2 \end{array}$	3×10^{-1}
Water	$H_2O:$	2×10^{-2}
Ethanol	$C_2H_5\ddot{O}H$	10^{-5}
Acetic acid	$CH_3C \begin{array}{l} \nearrow O: \\ \searrow OH \end{array}$	10^{-8}
Sulfuric acid	$(HO)_2S \begin{array}{l} \nearrow O: \\ \searrow O: \end{array}$	10^{-15}



diphenylamine



triphenylamine



a simple amide

C. Weak Bases Studied in Strong Acid Solutions

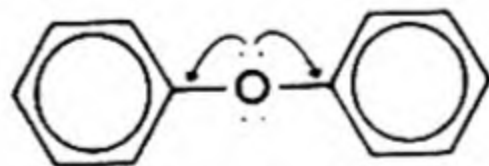
The basicity of alcohols, ethers, acids, esters, carbonyl compounds, phenols, and thio compounds is due to unshared electron pairs on oxygen and sulfur atoms. These compounds are, therefore, much less basic than similar nitrogen compounds. The strengths of these relatively weak bases cannot be measured in the usual fashion. Instead, the extent to which these substances accept protons from phosphoric acid or concentrated sulfuric acid is measured. The latter reaction is indicated in eq. (11).



When this reaction is complete, the substance generally dissolves in sulfuric acid. The extent of the reaction may also be determined by measurement of the extent of lowering of the freezing point in 100% sulfuric acid, where compounds which are strong bases in sulfuric acid give two particles (BH^+ and HSO_4^-) (sometimes further dissociation produces more) per mole of B added and compounds that are not basic give only one particle (B itself). Intermediate-strength bases gives values between 1 and 2. The value observed (moles of solute particles per formula weight of added solute) is called the van't Hoff i or ν factor (eq. 12).

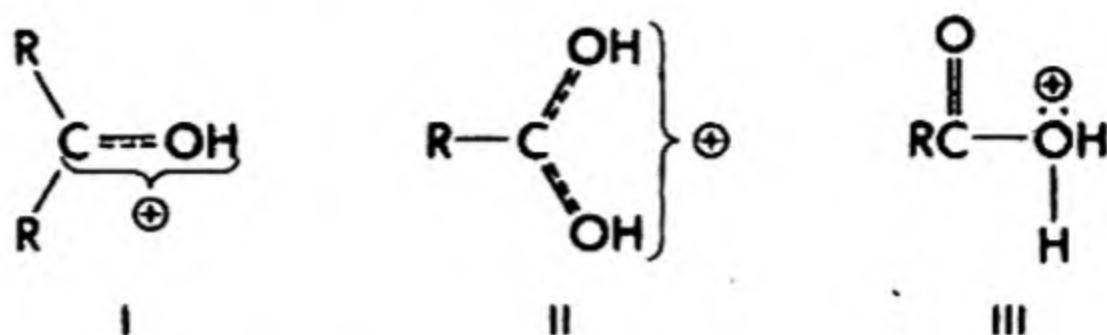
$$(12) \quad i = \Delta T_{f \text{ sample}} / \Delta T_{f \text{ undissociated compound}}$$

With one exception, all classes of compounds which have oxygen attached to carbon, and many sulfur compounds, are soluble in concentrated sulfuric acid. The exception again shows the effect of aromatic groups. Diaryl ethers have no measurable basicity. Here again, substantial delocalization energy would be lost in going from the base to the protonated species.

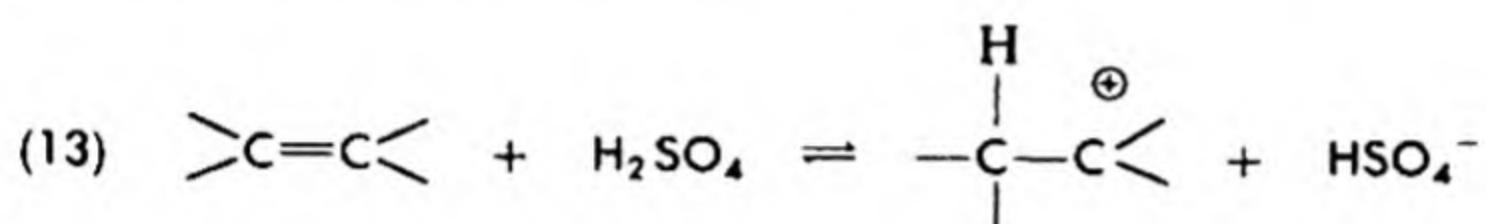


a diaryl ether

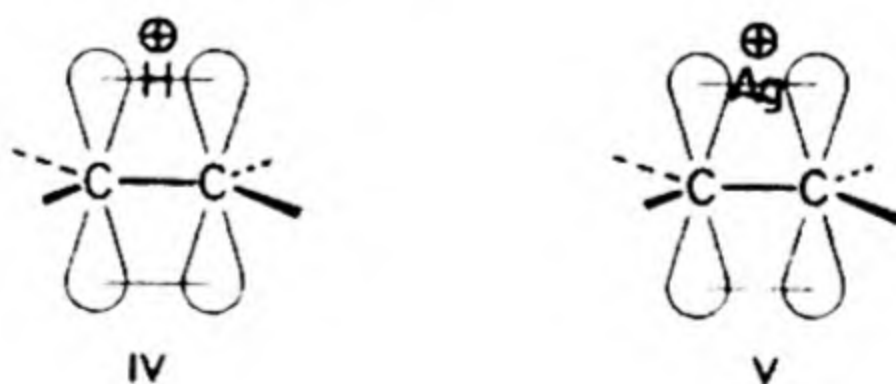
Carbonyl compounds are readily protonated on the oxygen atom (I). The positive charge is distributed over the oxygen and carbon atoms. Acids and esters are protonated in part on the carbonyl oxygen and in part on the hydroxyl or alkoxy oxygen (II and III); the former is probably far more stable, due to conjugative stabilization as in II.



Many olefins dissolve in concentrated sulfuric acid to give van't Hoff *i* factors of 2. The reaction is believed to involve the action of the olefin as a base to give its conjugate acid, which is a carbonium ion (eq. 13). The reaction is not rapidly reversible at low temperature, hence involves a more deep-seated change than the usual acid-base reaction. It has been suggested that an acid-base equilibrium involving a π complex (eq. 14) precedes the carbonium ion formation.

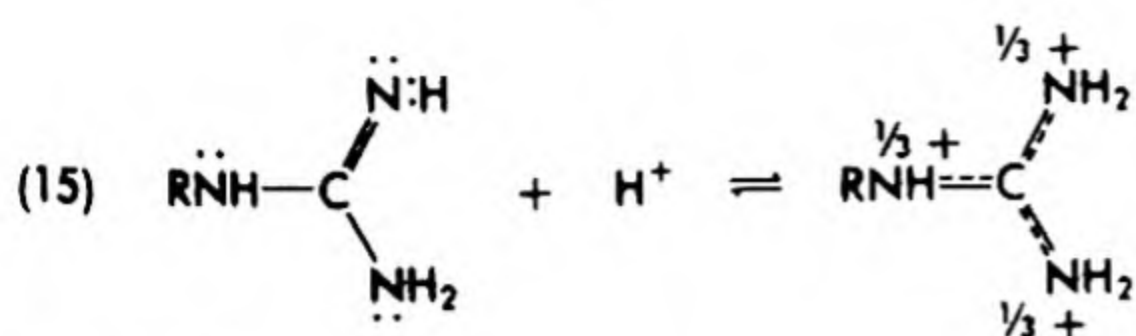


In a π complex, the hydrogen ion is considered to be buried in the π orbital of the double bond, IV. The involvement of these complexes is based on an analogy to stable, isolable π complexes between certain electrophilic substances (other examples: I_2 , Ag^+) and π orbitals of unsaturated and aromatic systems (e.g., V).

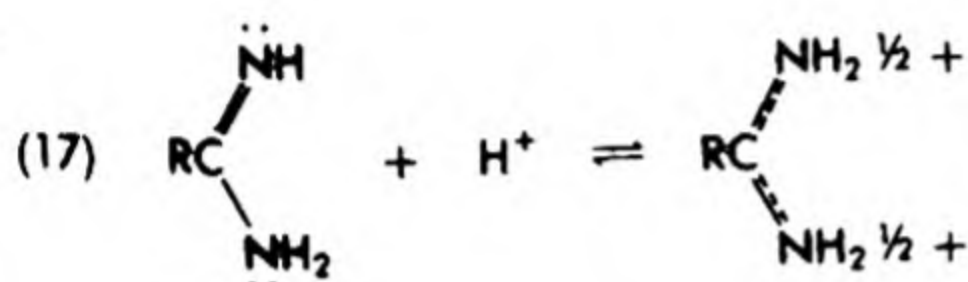
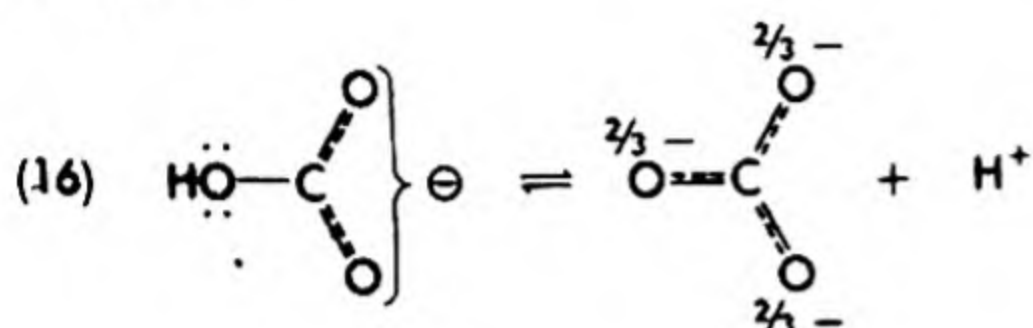


D. Strong Organic Bases

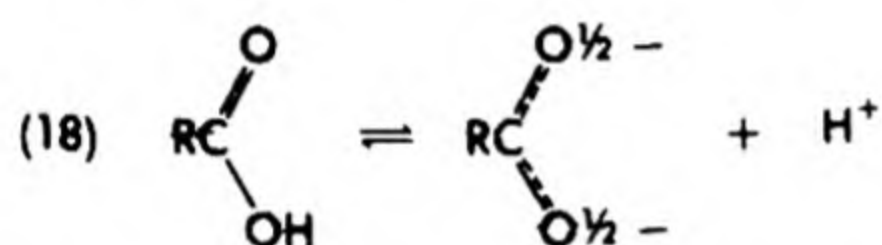
Among the very strong organic bases are guanidines and amidines. The stronger basicity of these compounds results from the greater electron delocalization permitted in the conjugate cation, where such delocalization does not involve separation of charge, as compared with the bases themselves, where delocalization is accompanied by charge separation and is therefore not as stabilizing (see eqs. 15-18).



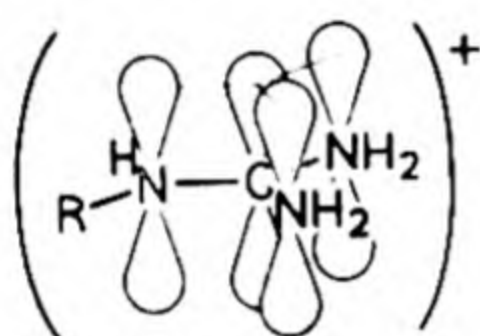
Compare:



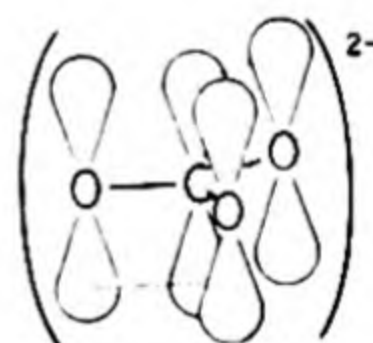
Compare:



The guanidinium ion has low-energy molecular orbitals very similar to those of the carbonate ion.

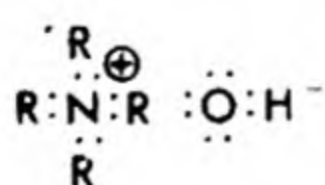


guanidinium ion

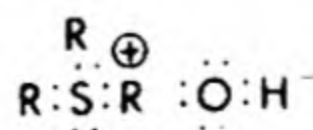


carbonate ion

Certain organic bases are ionic species, consisting of organic cations and hydroxide ions. These are completely dissociated in aqueous solution and exist as ionic species (ion pairs or aggregates) even in their pure solid states. Common examples are found in the quaternary ammonium hydroxides and the trialkylsulfonium hydroxides. In each of these classes the sulfur or nitrogen atom has an octet of electrons so that the hydroxide cannot form a covalent bond without involving higher energy orbitals.



quaternary ammonium hydroxides



trialkylsulfonium hydroxides

SUPPLEMENTARY READING

VanderWerf, C. A., *Acids, Bases and The Chemistry of the Covalent Bond*. Reinhold, New York, 1961. A short, inexpensive paperback which may serve well as a supplementary introduction to the next few chapters.

QUESTIONS AND PROBLEMS

- Compare the Arrhenius, Brønsted, and Lewis concepts of acids and bases. Point out their differences and their respective advantages and disadvantages.
- Arrange the following groups of acids in the order of decreasing acid strengths (e.g., $\text{HCl} > \text{HC}_2\text{H}_3\text{O}_2$).
 - acetic acid, fluoroacetic acid, difluoroacetic acid
 - propionic acid, α -chloropropionic acid, β -chloropropionic acid
 - benzoic acid, *m*-chlorobenzoic acid, *p*-chlorobenzoic acid
 - α -aminobutyric acid, α -mercaptobutyric acid, α -chlorobutyric acid
 - n*-amyl mercaptan, pentane-1-sulfonic acid, pentane-1-sulfinic acid
- Arrange the following groups of bases in the order of decreasing basic strengths (e.g., $\text{NaOH} > \text{NH}_3$).

a. ammonia, <i>n</i> -butylamine, aniline	phthalimide
b. aniline, <i>p</i> -nitroaniline, <i>p</i> -chloroaniline	d. acetamide, urea, guanidine
c. ethanolamine, acetamide,	e. ethyl ether, ethyl sulfide, diethylamine
- (a) Write all of the principal valence bond structures for *ortho*, *meta*, and *para* nitrophenoxide ions.
 (b) Explain why *m*-nitrophenol is a weaker acid than *p*-nitrophenol.
- Show how the following salts can be prepared conveniently for use in synthesis. Use the cheapest source of metal ions possible (e.g., $\text{NaCl} = \$0.01/\text{lb.}$, $\text{Na}_2\text{CO}_3 = \$0.03/\text{lb.}$, $\text{NaHCO}_3 = \$0.04/\text{lb.}$, $\text{NaOH} = \$0.08/\text{lb.}$, $\text{Na} = \$0.19/\text{lb.}$ in commercial lots).

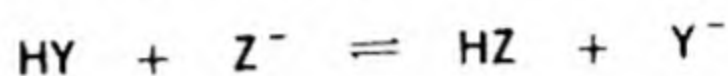
a. monosodium acetylide from acetylene	benzenesulfonic acid
b. calcium acetylide, industrial method	h. potassium phthalimide from phthalimide
c. sodium ethoxide from ethanol	i. diethyl sodiomalonate from diethyl malonate
d. sodamide from ammonia	j. sodium ethyl sulfide from ethanethiol
e. sodium phenoxide from phenol	k. aluminum isopropoxide from isopropyl alcohol
f. calcium acetate from acetic acid	
g. sodium benzenesulfonate from	
- Which of the salts listed in Problem 5 could be recrystallized from water?
- List those of the following compounds which show the properties below. Guanidine, 4-ethylpyridine, dibutylamine, aniline, diphenylamine, triphenylamine, dibutyl sulfide, thiophenol, dibutyl ether, *p*-butylphenol.
 - Give basic reaction to moist red litmus paper
 - Dissolve completely in dilute hydrochloric acid
 - Dissolve completely in concentrated hydrochloric acid, but not dilute hydrochloric acid

d. Dissolve completely in concentrated sulfuric acid, but not concentrated hydrochloric acid

8. (a) Write all of the principal valence bond structures for *meta* and *para* methoxybenzoic acids.

(b) Explain why the *meta* acid is stronger than benzoic acid, while the *para* acid is weaker.

9. Calculate the fraction of reagent that has reacted, $[Y^-]/([HY] + [Y^-])$, at equilibrium if the reagent acid is 100 times as strong as the product acid, where equal amounts of 1M solutions of HY and Z^- are mixed.



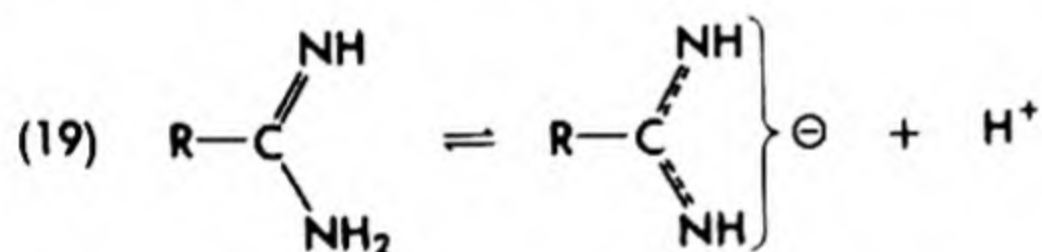
$$K_a \text{ for HY} = 100 \times K_a \text{ for HZ}$$

What effect does dilution of the mixture have on the completeness of reaction at equilibrium (provided no special solvent effects change the equilibrium constant)?

10. Define and illustrate the following terms.

- | | |
|-----------------------|-------------------------------|
| a. bond polarization | f. mesomeric stabilization |
| b. conjugate pair | g. polar molecule |
| c. conjugative effect | h. protonation |
| d. inductive effect | i. van't Hoff <i>i</i> factor |
| e. Lewis acid | |

11. Why is an amidine generally a base (eq. 17), and not an acid (eq. 19)? Under what conditions would an amidine be expected to act as an acid?



Compare (with equations) to acetic acid, which is a base in pure sulfuric acid.

12. Write valence bond structures to illustrate the stabilization of the dinitromethane conjugate anion by resonance.



Factors Influencing Chemical Reactions and Reactivities

11-1 BASIC PRINCIPLES

Stress on the similarities in behavior of water and alcohols, ammonia and amines, and inorganic and organic acids has evinced the identity of the basic principles of both organic and inorganic reactions.

It must be clearly apparent by this time that organic chemistry is a vast and complex field. To avoid Liebig's feeling (1823) that this field is a trackless jungle, it is necessary to utilize all possible unification available from the basic principles of chemistry. Nothing has succeeded in lending credibility and unification to organic reactions as much as the modern study of *reaction mechanisms*, the pathways by which reactions *appear* to occur. Since the mature student has by this time mastered the properties of the simple functional groups, he is ready to look into the intricacies of these reactions and see, in far greater detail, yet with overall greater simplicity, why organic compounds behave as they do.

While some modest predictive skill may develop, it is expected that the main utility of mechanism for now will lie in the explanation and classification of reactions.

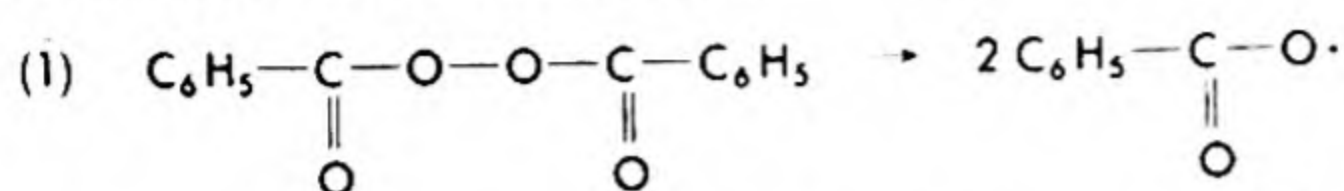
11-2 FUNDAMENTAL REACTION TYPES

Chemical reactions are examples of or combinations of a few basic types which occur in a variety of manifestations. Recognition of these types greatly simplifies study of the great diversity of organic reactions.

A. Homolysis, Combination, and Dissociation Energies

When a molecule dissociates in such a way as to unpair and separate the electrons in a covalent bond, as in eq. (1), the reaction is termed *homolysis*. The fragments, which thus have an odd or unpaired electron each, are called *free radicals*. These are highly reactive. Hence, free radicals ordinarily have but transitory existence. Certain free radicals are stabilized by electronic interactions in the molecule; certain others have been

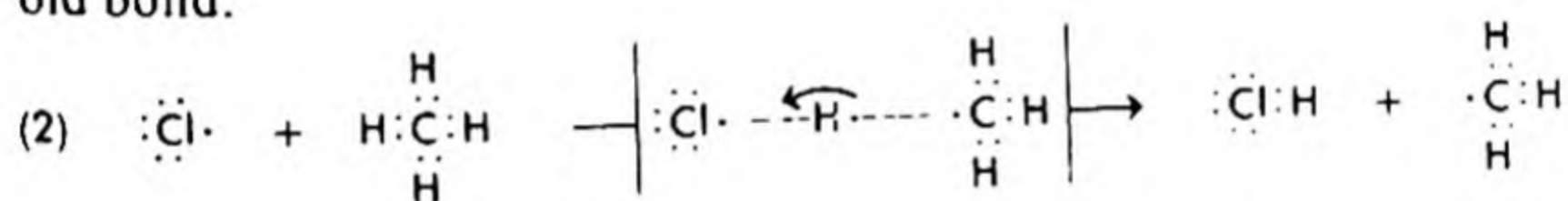
stored for limited times in the solid state, either at very low temperatures or enmeshed in a solid polymer. These, however, are exceptional cases.



Eq. (1) is an example of homolysis; the product fragments are free radicals. The energy required for this reaction is the dissociation energy for this particular O—O bond. This cleavage of benzoyl peroxide is a convenient source of free radicals for such reactions as the commercially important formation of plastics (polymers) from small molecules.

The reverse of homolysis is *combination*. The combination of two free radicals must involve the disposition of excess energy (at least equal to the dissociation energy). This energy may be transferred to a third body, or if the radicals are complex, may be divided among the various bonds in the resulting molecule (rotational and vibrational energies).

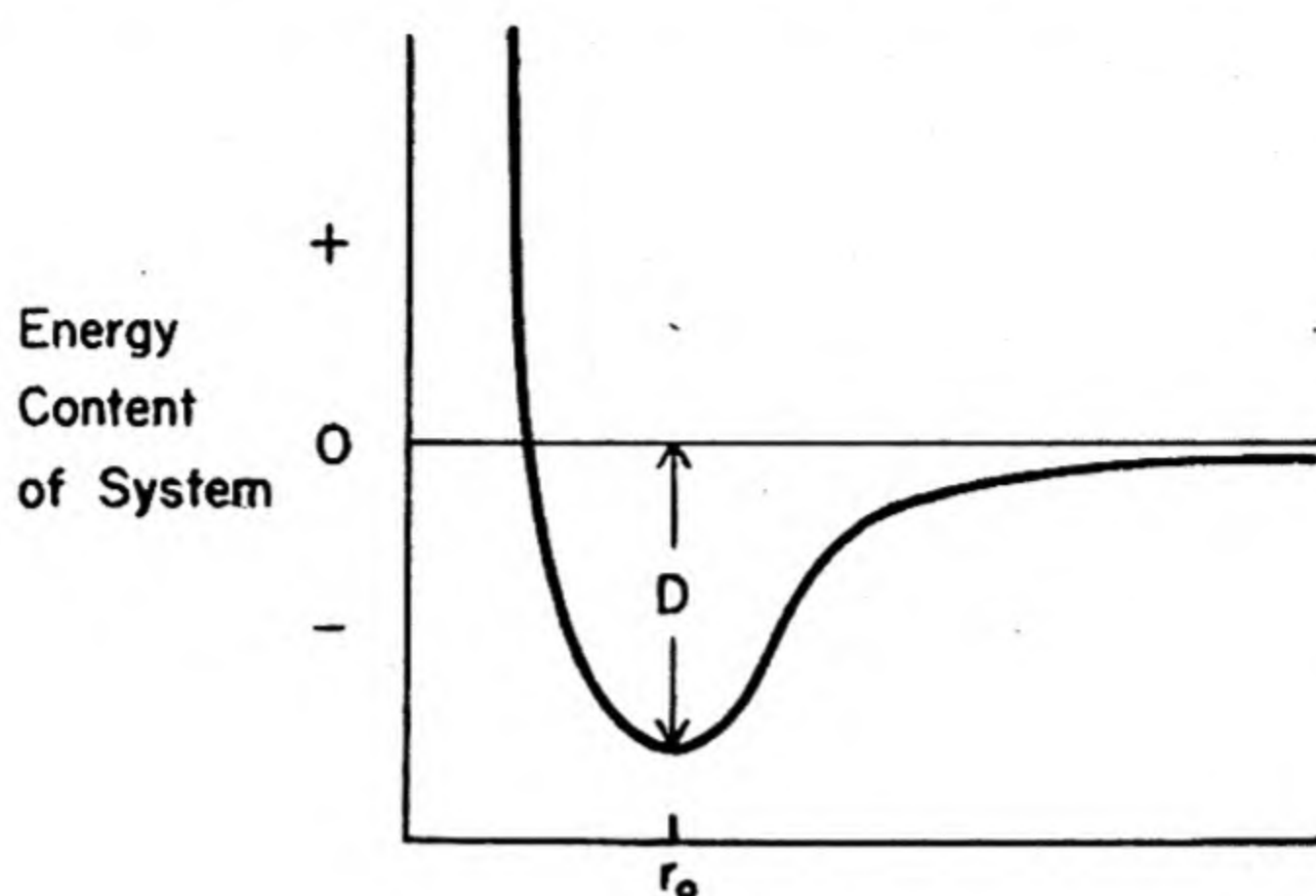
Another reaction of free radicals involves direct displacement by a radical on one atom of a covalent bond (eq. 2). In this process the new bond formation is *concerted* (simultaneous) with the homolysis of the old bond.



Reactions involving free radicals are usually called homolytic, or simply free radical, reactions. For these types of reactions, bond dissociation energies directly influence the reaction course and reaction rate.

The energy of a bond between two atoms or groups, A and B, is shown in Fig. 11-1. In this figure, r_0 represents the normal bond distance between A and B. When these two atoms are separated by a large distance, there is no interaction. As they are brought together, the energy decreases (system is more stable). The energy content reaches a minimum at r_0 and then increases rapidly due to nuclear repulsions. The energy required to dissociate the bond into the fragments A and B, which are neutral if the particle A—B is a molecule, is called the *bond dissociation energy* and is represented by the symbol D .


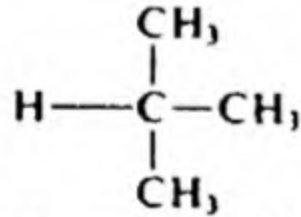
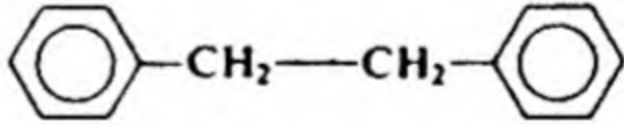
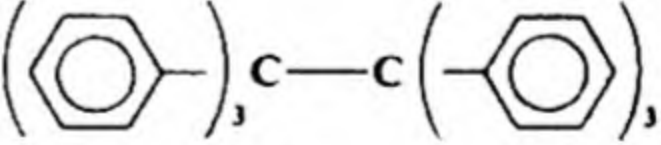
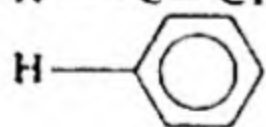




Ease of halogenation of alkanes and of substituted alkanes depends largely on the relationship between the C—H dissociation energy and the H—Cl or H—Br dissociation energy. In general, the lower the C—H dissociation energy, the more rapidly halogenation occurs at that position, as the rate of halogenation at a position depends upon the ease of attack of a halogen atom on the hydrogen of a carbon-hydrogen bond. The variation of dissociation energies with position of hydrogen is given in Table 11-1.



Distance between Groups A and B

Fig. 11-1. Morse Curve for Bond Dissociation Energy (see §4-1D).

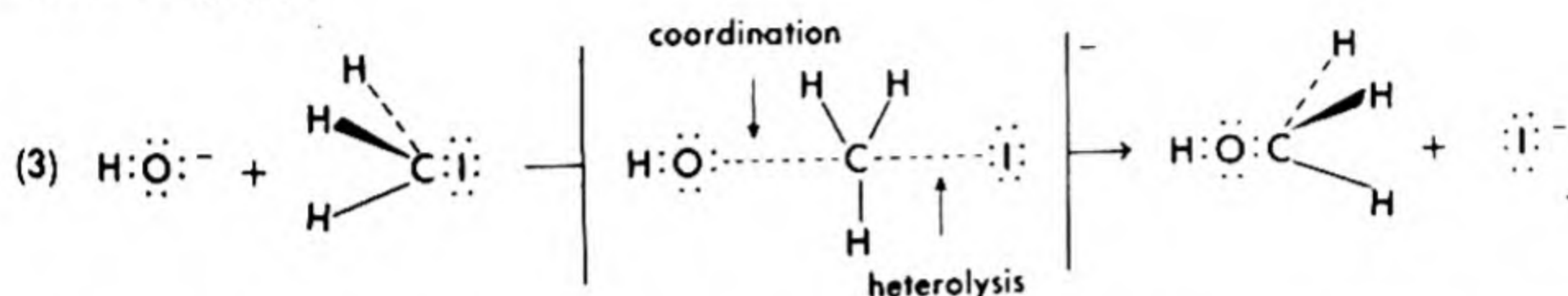
TABLE 11-1. Bond Dissociation Energies^a

Bond	<i>D</i> ., kcal./mole	Bond	<i>D</i> ., kcal./mole
H—CH ₃	101	H—OH	116
H—CH ₂ —CH ₃	96	H—O·	103
H—CH ₂ CH ₂ CH ₃	100	H ₃ C—CH ₃	83
H—CH(CH ₃)—CH ₃	94	H ₃ C—CH ₂ CH=CH ₂	62
H—CH ₂ CH ₂ CH ₂ CH ₃	101	H ₃ C—CH ₂ — 	63
	89	• 	47
H—CH=CH ₂	< 121		10-12 in solution.
H—CH ₂ —CH=CH ₂	77 ^b		
H—C≡CH	< 121	H ₃ C—CH=O	75
H— 	102	Br—CH ₃	67
		Br— 	71
H—CH ₂ — 	78		
H—CH()—R	75	Br—CH ₂ — 	51

^aT. L. Cottrell, *The Strengths of Chemical Bonds*, 2nd Ed., Butterworth, London (1958).^bA. H. Schon and M. Swarc, *Proc. Roy. Soc. (London)*, Ser. A, 202, 263 (1950).

B. Heterolysis and Coordination

When a molecule dissociates in such a way that both of the shared electrons of the broken bond go with one of the fragments, the reaction is termed *heterolysis*. The reverse of this process, that is, the attachment of an electron-pair donor to an electron-pair acceptor, is called *coordination*. Many reactions involve these two separate stages. However, in many others, the two stages are merged so that the formation of one bond accompanies the breaking of the other. An example of this direct displacement is eq. (3).



Organic chemists term reactions which involve electron-pair transfers as heterolytic or "ionic" reactions, distinguishing them in this way from the homolytic or free-radical reactions, which involve electron pairing and unpairing.

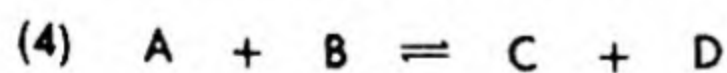
C. Electron Transfer

The balance of reactions are electron-transfer reactions. Since these are most typically reactions of free elements or ions, they occupy a less important position in organic chemistry than in inorganic chemistry.

11-3 CHEMICAL EQUILIBRIA AND REACTION RATES

A. Equilibrium Constants

Whether a reaction can occur depends upon two things. First, the products must be more stable than or of the same order of stability as the reactants. Second, there must be a suitable pathway between reactants and products such that the reaction may proceed at an appreciable rate. The relative stabilities of products and reactants are related to the equilibrium constant. For example, in the reaction described by eq. (4), the equilibrium constant, K , is given by eq. (5). If the numerical value of this constant is larger than one, $C + D$ must be more stable than $A + B$, and

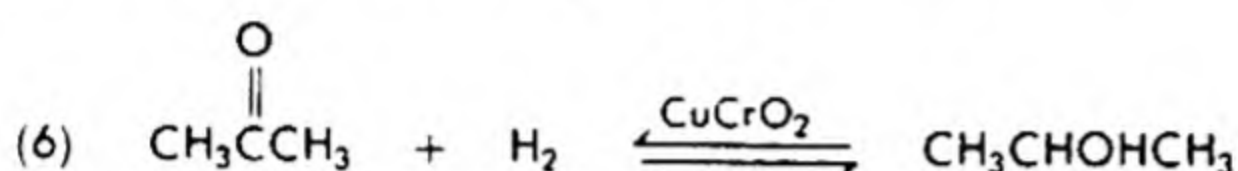


$$(5) \quad K = \frac{[C][D]}{[A][B]}$$

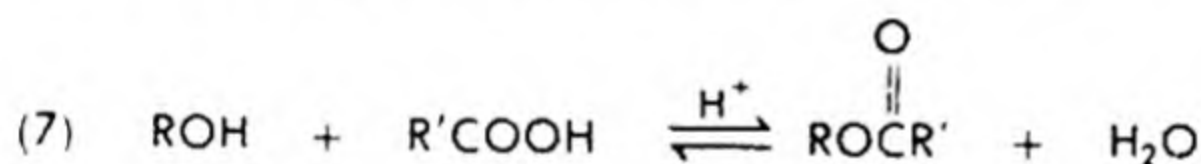
if the reaction proceeds rapidly enough under conditions where C and D do not react further, the yield of the products is substantial. We have already discussed the effect of stabilization of reactants or of products

upon equilibrium constants for ionization of acids and bases (see §7-3A(2), §10-2A, §10-2D, and §10-2E). Similar effects may be observed in other chemical equilibria.

The equilibrium constants of reactions vary with temperature so that it is possible to control the extent of reaction in certain cases by changing the reaction temperature. An example of this principle, and also of the principle of mass action, is shown in eq. (6), which proceeds to the right at relatively low temperatures and at high hydrogen pressures, but to the left at 300° and low hydrogen pressures.



The principle of mass action is often used to force a reaction closer to completion. A large excess of one (usually the cheaper) reagent may be used. For example, in the formation of esters, an excess either of alcohol or of organic acid is profitable (eq. 7) for an increase in [A] or [B] forces [C] and [D] to increase to keep K constant at equilibrium. Similarly, removal of either product C or D from the reaction mixture, by distillation, if one of these is more volatile than A and B, or by precipitation, if this can be accomplished by conducting the reaction in a suitable solvent, may serve to bring the reaction to completion.



B. Reactivity and Rates of Reaction

Even assuming that a reaction has a very favorable equilibrium constant, there must be a pathway that reactants can traverse readily to become products if the reaction is to proceed at a reasonable rate. For this reason, we shall have a considerable interest in the study of reaction pathways, called *reaction mechanisms*, as well as in the factors that control reaction rates or reactivities of molecules.

(1) *Reaction Order.* In a reaction, say between A and B to give C, one of several possibilities is that A and B react directly with each other, without the involvement of intermediates, to yield C. In such a case, the rate of reaction, which could be followed by noting how rapidly the concentrations of A and B decrease or how rapidly that of C increases, is given by eq. (8)

$$(8) \quad \text{rate} = k[\text{A}][\text{B}]$$

where k is the specific reaction rate constant, and [A] is concentration of A in moles per liter. The larger k , the faster the reaction proceeds. Increasing the temperature increases k , and changes in solvent usually modify k .

The rate of this reaction depends not only on the proportionality constant k , but also on the concentrations of A and B. Increasing [A] or [B] increases the reaction rate, but does not change the value of k for this reaction. A reaction such as this is called a second-order reaction and is dependent upon [A] to the *first* power and [B] to the *first* power—total order, two. Another example of a second-order reaction is given in eq. (9). There are many examples of first-order reactions, such as given in eq. (10) or of third-order reactions, as indicated in eqs. (11) through (13).

$$(9) \quad \text{rate} = k[A]^2$$

$$(10) \quad \text{rate} = k[A]$$

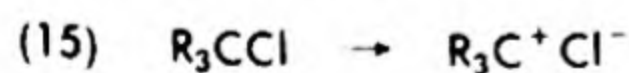
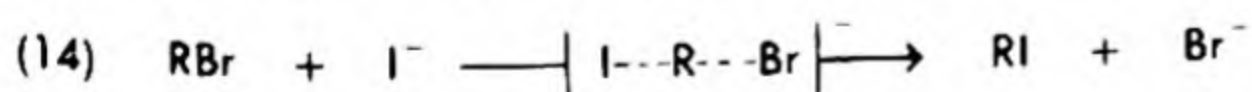
$$(11) \quad \text{rate} = k[A][B][C]$$

$$(12) \quad \text{rate} = k[A]^2[B]$$

$$(13) \quad \text{rate} = k[A]^3$$

The total of the powers, n , of concentrations of reagents is called the *order* of the reaction, or conversely, the reaction is called an n 'th-order reaction. The order of the reaction is not generally what one might anticipate from the stoichiometry of the overall reaction. Knowledge of the reaction order is of prime importance in determining the mechanism of a reaction. This can be done readily by varying the concentration of one reagent, such as A. If [A] is doubled, and the rate is unaffected, the reaction is said to be zero order in A. If the rate is doubled, the reaction is first-order in A, if the rate is quadrupled, it is second-order in A, and so forth. This is repeated for all reagents to determine not only the total order, but also the order in each reagent. The mechanism for the reaction must be consistent with the experimental reaction order.

(2) *Reaction Molecularity.* The order of a reaction is an experimentally determined quantity which depends on reaction molecularity, but is not necessarily identical to it. *Reaction molecularity* is the number of molecules (or ions) making or breaking covalent bonds in a reaction. Thus, the reaction represented by eq. (14) is bimolecular; that represented by eq. (15) is unimolecular. In §11-3E it is noted that the rate of a sequence of reactions depends on the slowest step. The molecularity of the overall reaction is considered to be that of the slow (rate-determining) step.



(3) *The Collision Theory of Reaction Rates.* From measurements of rates of reaction, and with experimental knowledge of reaction orders, it is possible to calculate the specific rate constant, k , for a given reaction. As we

will be concerned with the effect of structure of organic reagents upon the value of k , it is of interest to consider two theories of reaction rates.

One approach is the *collision theory*, which states that molecules react only when they collide, and then only when they contain at least a sufficient quantity of energy, called the *activation energy*, E_a . The frequency of fruitful collisions is calculated from the kinetic collision rate, Z , and the fraction of molecules that are activated, $e^{-E_a/RT}$, in which e is the base of natural logarithms, R a universal constant, and T the absolute temperature. Also involved is a probability factor, P , which takes into consideration that molecules must be suitably oriented to react when they collide, and that perhaps not all favorable collisions lead to products. The overall collision theory equation for the rate constant is eq. (16).

$$(16) \quad k = PZe^{-E_a/RT}$$

In logarithmic form this becomes eq. (17). A plot of $\log k$ vs. $1/T$ gives a straight line from the slope of which one may determine the activation energy, E_a , for the reaction. The distribution of energies of individual molecules at different temperatures, called the Boltzmann distribution, is shown in Fig. 11-2. Most of the molecules have energies close to the

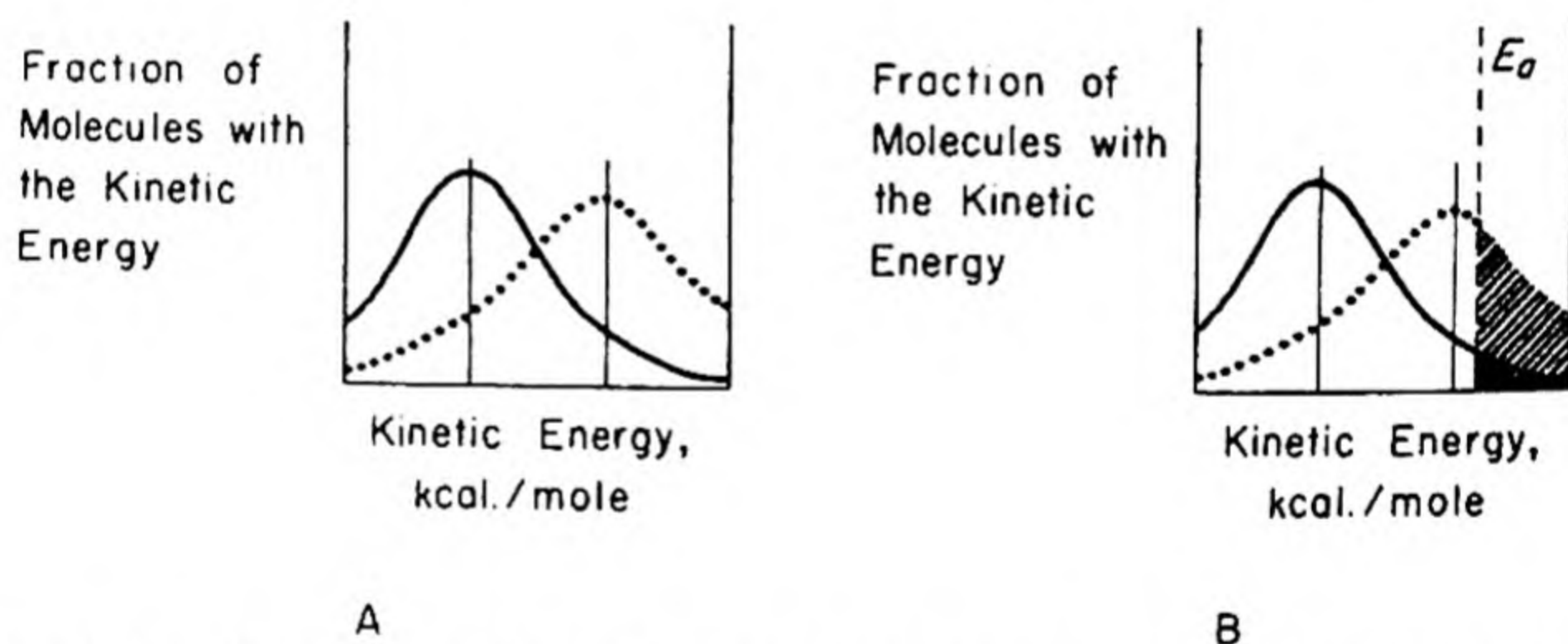


Fig. 11-2. Effect of Temperature on Activation of Molecules. (A) Distribution of Kinetic Energies of Molecules:—at 20°, ... at 100°, (B) proportion of Molecules with Activation Energy; solid black, 20°, hatched plus black, 100°.

average with a small fraction having much less or much more than the average.

$$(17) \quad \log k = \log PZ - \frac{E_a}{2.303 RT}$$

C. The Transition State Theory of Reaction Rates

Although the older collision theory was quite useful, it has been replaced almost entirely in theoretical organic chemistry by the *transition*

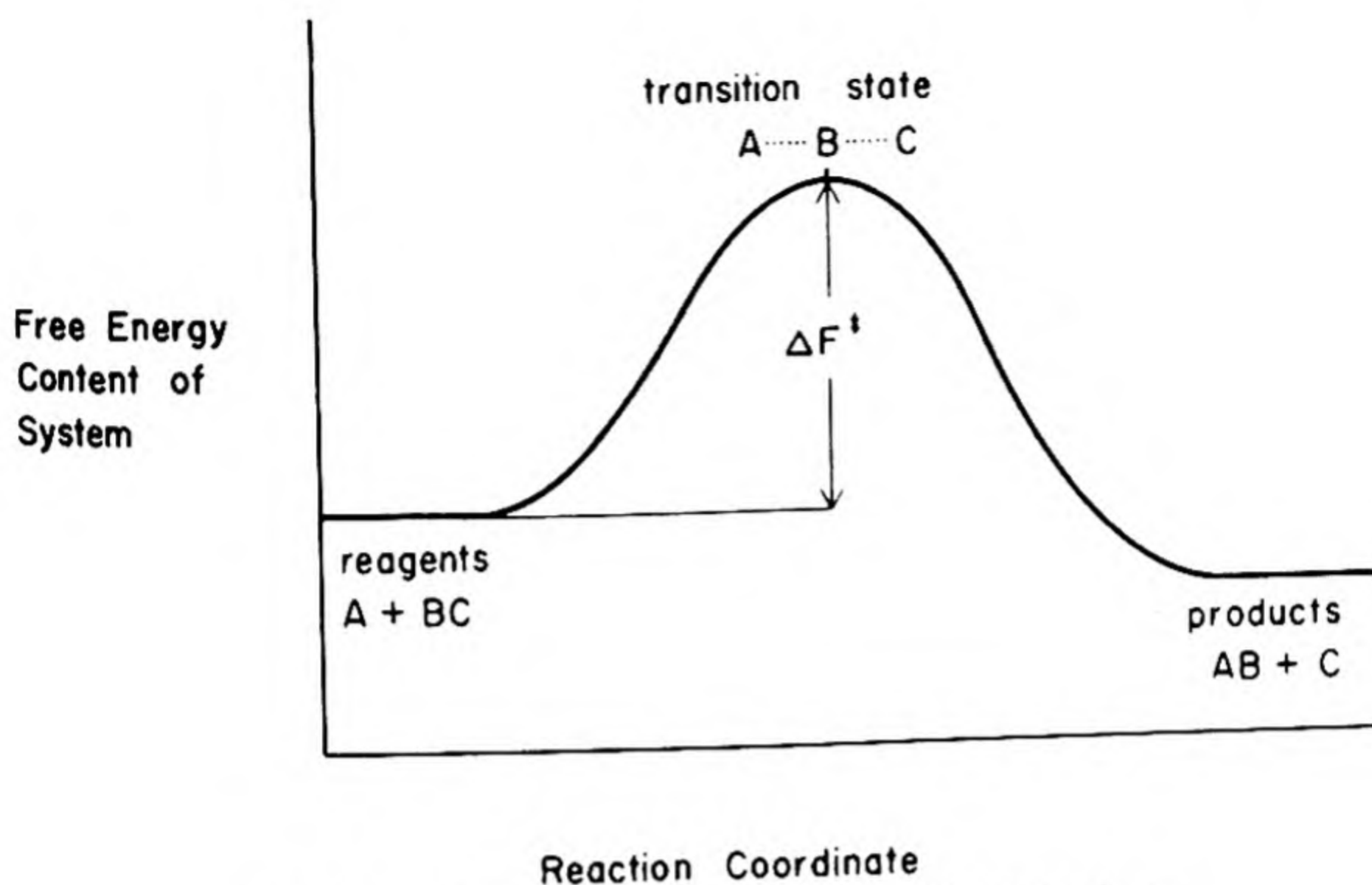


Fig. 11-3. Energy Diagram for Single-Step Reaction.

state theory. If we assume a reaction between A and BC to give AB and C directly and without the intervention of intermediates, we may represent this reaction as in Fig. 11-3. When A attacks BC, as the A—B bond is being formed, the B—C bond is being stretched. At the beginning of the reaction there is no A—B bond at all and the B—C bond is at the normal bond distance. At the end of the reaction there is no B—C bond and the A—B bond is at its normal bond distance. At other positions along the reaction coordinate (Fig. 11-3), each bond may be considered as a partial one with the A—B and B—C bond distances both greater than those in the normal nonreacting bonds.

Figures 11-3 and 11-4 show that, as the A—B bond begins to form, less energy is released than is absorbed by the corresponding partial separation of the B—C bond. Consequently, the energy of the system rises as the bond transfer begins, achieves a maximum where the system is least stable, then falls again as the products near formation. The final separation of the B—C bond absorbs less energy than the corresponding final formation of the A—B bond releases. This is true regardless of the pathway of the reaction (heterolytic or free radical), since between any set of reagents and their products must occur some transient complex of lesser stability. The *maximum point* on the energy diagram for the reaction (Fig. 11-3) represents what is called the *transition state* of the reaction.

If it were possible to know the structure and properties of the transition state (TS), so that one could calculate its free energy, then one could calculate the rate of reaction from this and from knowledge of the free

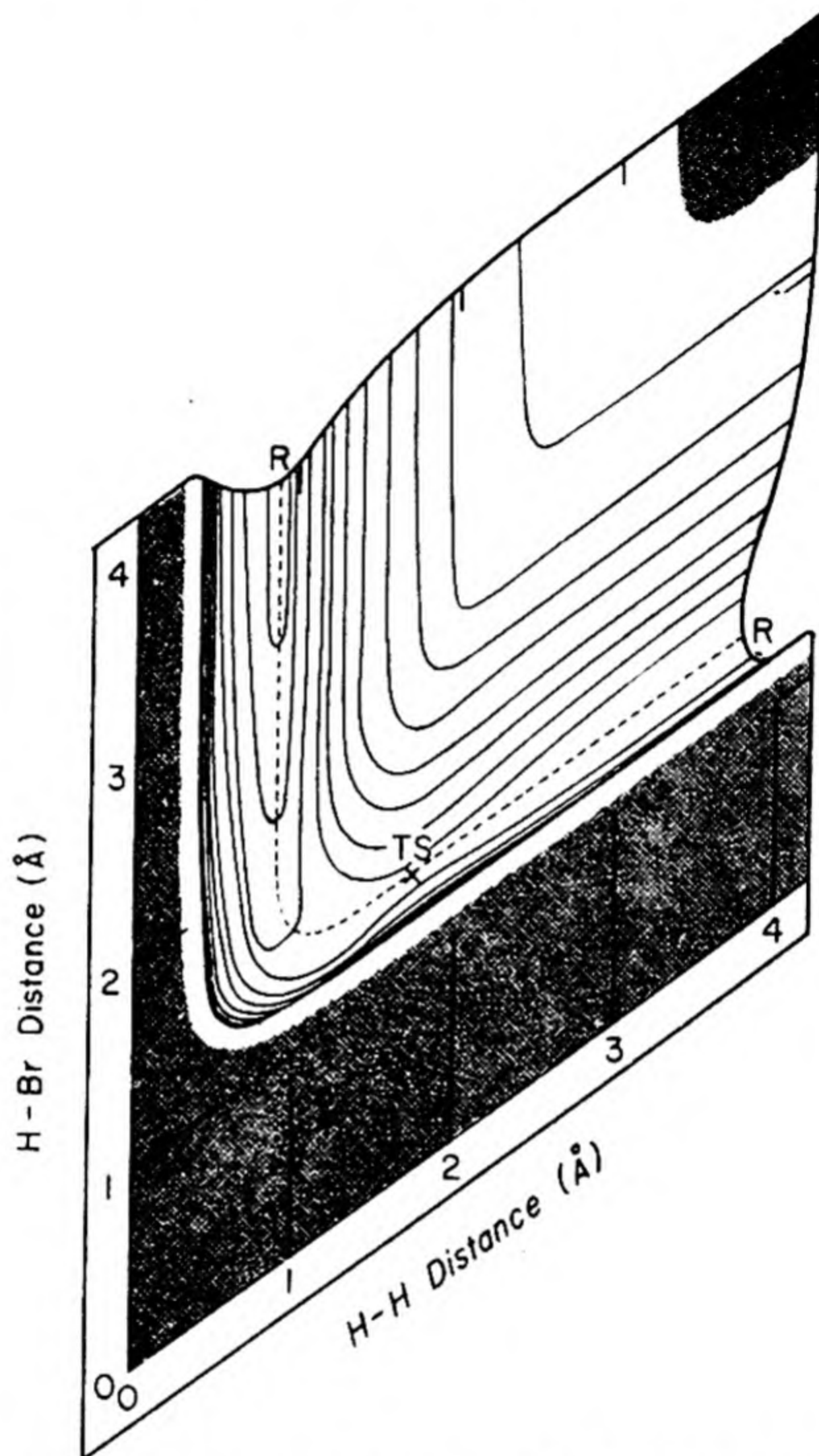


Fig. 11-4. Perspective Contour Model of Energy Content of System H, H, Br.

energy of the reactants. However, the transition state is not a stable, isolable species, but in fact is the least stable point on the path that the system traverses. In practice it is possible only to make educated guesses as to its nature.

The pathway of a reaction on an energy diagram is called the *reaction coordinate* (R---R in Fig. 11-4). It requires a three-dimensional model (Fig. 11-4: system H, H, Br) to give the energies related to the two intergroup distances. Straightening out the reaction coordinate into a plane diagram gives the related energy diagram for the usual transition state (Fig. 11-5, see also Fig. 11-3).

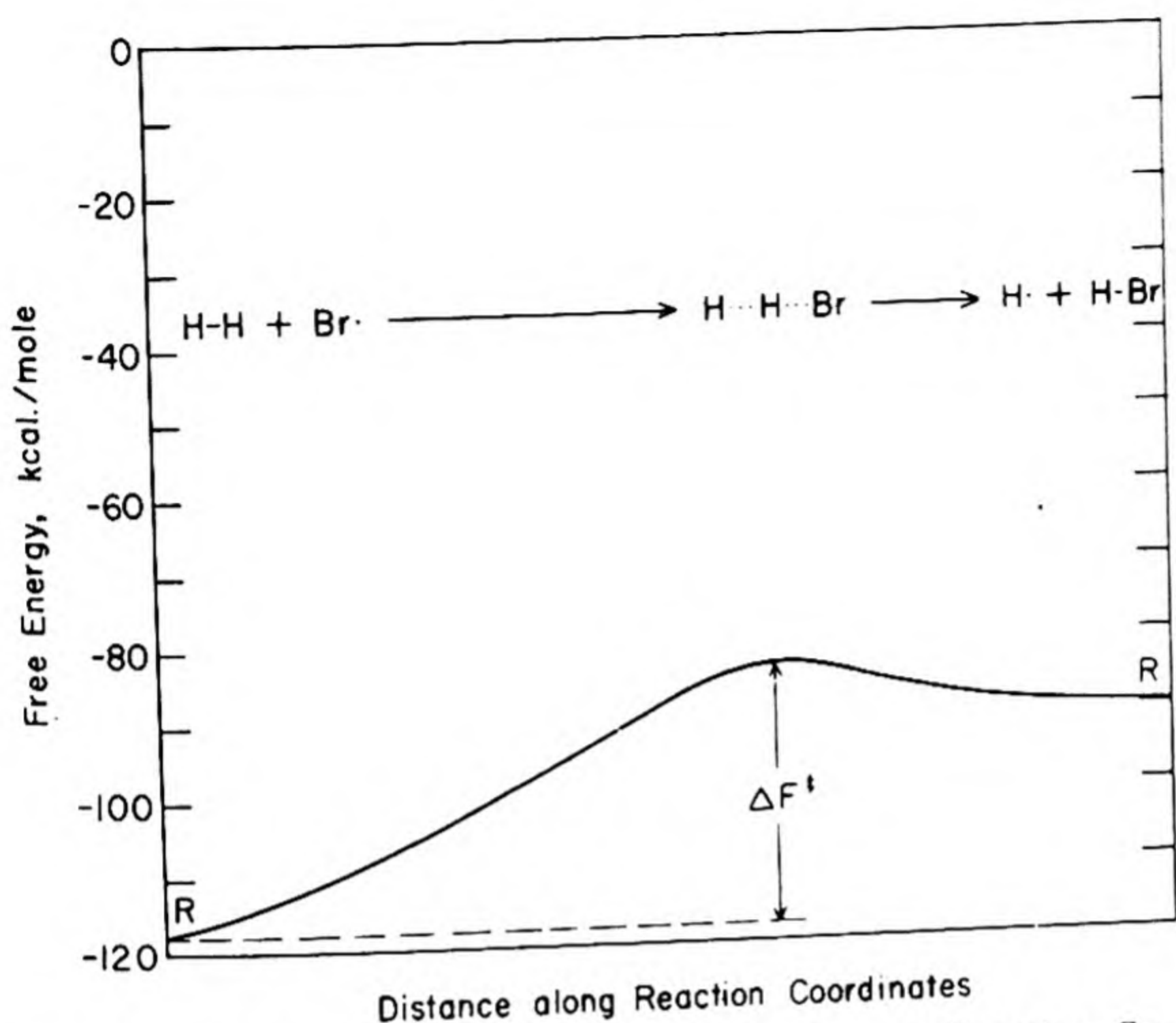


Fig. 11-5. Energy Content as Related to Position on Reaction Coordinate, R---R in Fig. 11-4. ΔF^\ddagger , activation energy of reaction proceeding to the right as shown.

The difference in energy between the transition state and the reactants represents the energy barrier over which the reaction must proceed. The higher the energy barrier, the slower the reaction, since fewer molecules possess the required energy (see Fig. 11-2).

The transition state has a structure between that of the reactants and that of the products. It resembles reactants more than products when the transition state is close (in reaction coordinate) to the reactants (Fig. 11-6A) and products more than reactants when the converse is true (Fig. 11-6B). The former situation is generally true in highly exergonic (energy-liberating) systems and the latter in highly endergonic (energy-absorbing) systems.

If one chooses a proper model for the transition state, the effects of groups on its stability can be predicted. If a certain change in solvent or nature of the reactants stabilizes the transition state more than it does the reactants (Fig. 11-7A) then the reaction goes faster. If another change stabilizes reactants more than transition state, the activation free energy is increased (Fig. 11-7B) and the reaction rate decreased. The model can be modified at will until it best fits the experimental data.

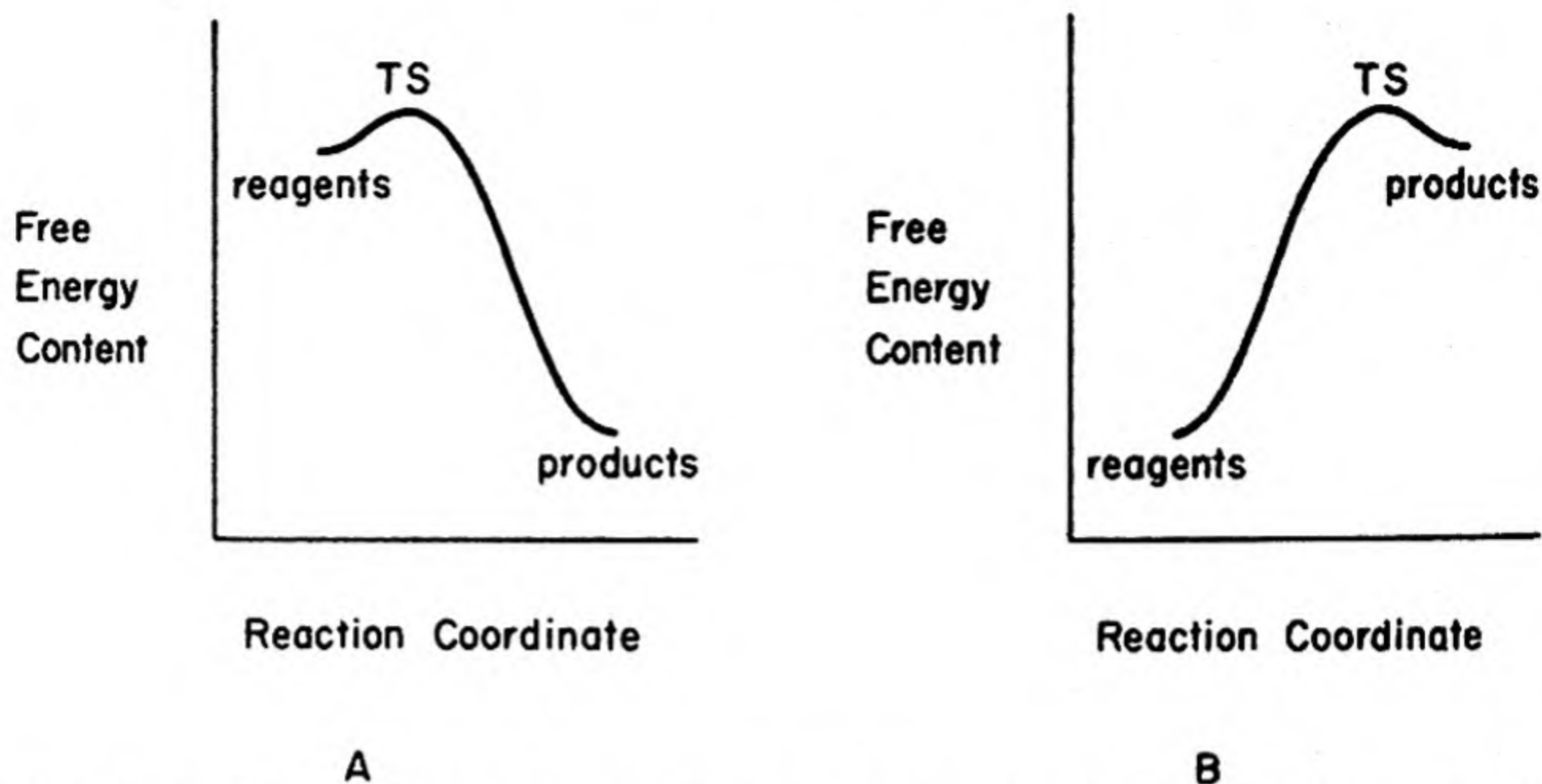


Fig. 11-6. Energy Diagrams for Reactions with (A) Large negative ΔF and (B) Large positive ΔF . (A) Exergonic reaction in which TS resembles reagents. (B) Endergonic reaction in which TS resembles products.

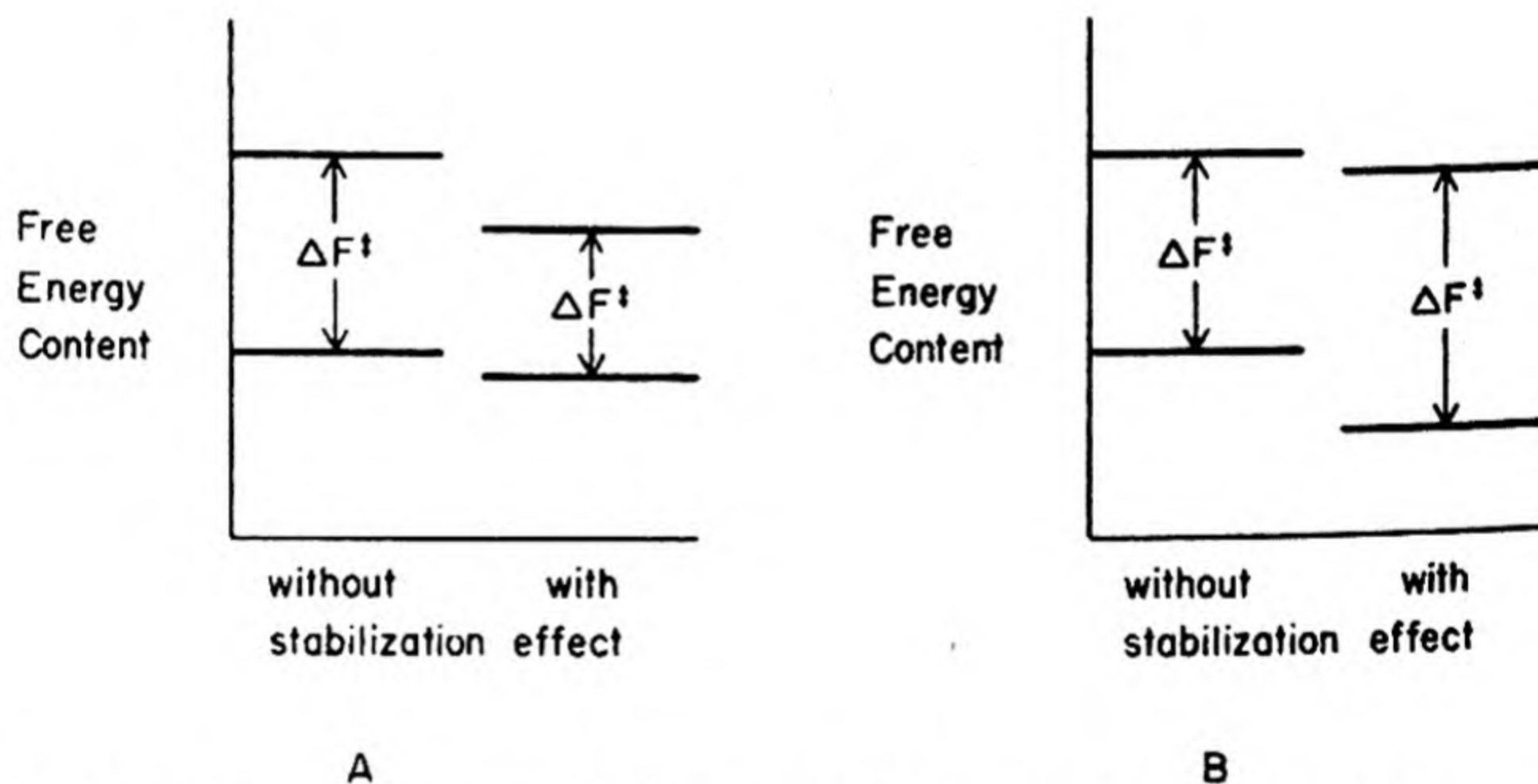


Fig. 11-7. Energy Diagrams for Effects of Stabilization of Reagent and Transition State on Free Energy of Activation. (A) Transition state stabilized more than reagents, ΔF^\ddagger decreased. (B) Reagents stabilized more than transition state, ΔF^\ddagger increased.

D. Quantitative Treatment of Equilibria

A branch of physical chemistry called thermodynamics is concerned with the quantitative treatment of equilibrium energy relationships. The following equation can be derived to describe any chemical equilibrium.

$$(18) \quad \begin{array}{ccccc} -\Delta F & = & T\Delta S & - & \Delta H \\ \text{Driving force} & = & \text{Energy involved in} & - & \text{Heat put into} \\ \text{(total work done} & & \text{change of freedom} & & \text{the reaction} \\ \text{by the reaction;} & & \text{of system} & & \\ \text{decrease in chemical} & & & & \\ \text{potential energy)} & & & & \end{array}$$

In eq. (18), ΔF is the change in *free energy* from reactants to products, ΔH is the *heat of reaction*, and ΔS is the change in *entropy*. The free energy is a measure of the driving force of the reaction and is *negative* for *exergonic* reactions, which proceed spontaneously, as can be seen from eq. (19)

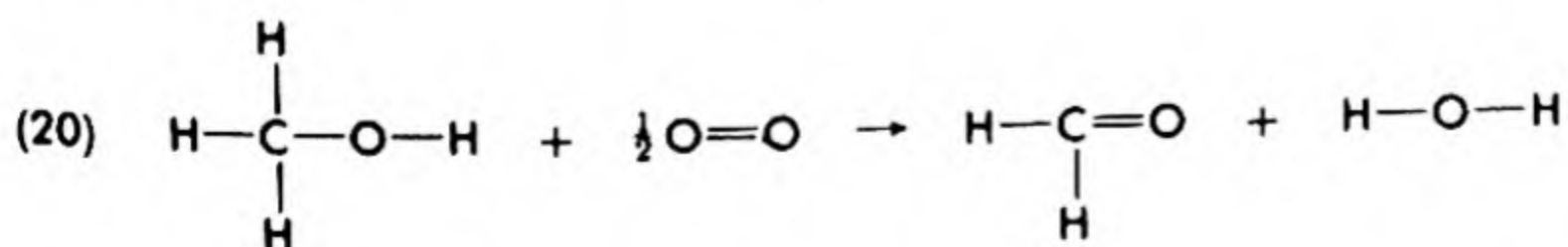
$$(19) \quad -\Delta F = 2.3 RT \log K$$

where R is a constant, T is the absolute temperature, and K is the equilibrium constant for the reaction (see eq. 5). ΔH is the heat of the reaction and can be measured in a calorimeter or estimated as described below. While the terms exergonic and exothermic are sometimes interchanged, the former term refers to a negative ΔF , while the latter refers to a negative ΔH . Thus, some of the potential energy of the reaction increases or decreases the randomness of the system; the balance produces heat. The driving force, $-\Delta F$, is the total decrease in chemical potential energy when a specified number of moles of reactants is converted to the equivalent number of moles of products. If the chemical potential energy increases (endergonic reaction), work must be done to make the reaction occur, and it is not spontaneous.

The change in entropy of a reaction, ΔS , is a measure of the change in freedom or randomness of a system. The natural tendency of systems is to become as random as possible (high entropy content). Any restriction upon this (such as lining up molecules or atoms in a molecule in a given conformation) lowers the entropy and correspondingly makes ΔF more *positive* (eq. 18). This then reduces the driving force of a reaction.

Since $T\Delta S$ is temperature dependent, it is possible to make an endergonic reaction become exergonic by a suitable change in temperature.

One way to estimate the heat of a reaction is to calculate the difference in bond energies of reactants and products from the data of Table 11-2. For the oxidation of methanol to formaldehyde, the following calculation is involved.



Bonds broken: $\frac{1}{2} \text{O}=\text{O} = 59 \text{ kcal./mole}$
 $\text{O}-\text{H} = 111$
 $\text{C}-\text{O} = 86$
 $\text{C}-\text{H} = 99$

Energy input: 355 kcal./mole

Bonds formed: $\text{C}=\text{O} = 166 \text{ kcal./mole}$
 $2 \text{O}-\text{H} = 222$

Energy release: 388 kcal./mole

Heat of reaction, ΔH : -33 kcal./mole (exothermic)

This is an approximate method, which works fairly well for non-conjugated systems. Resonance completely upsets calculations based on bond energies. While increments due to conjugated systems can be applied, they are not very precise.

TABLE 11-2. Bond Energies^a

Bond	Energy, kcal./mole	Bond	Energy, kcal./mole	Bond	Energy, kcal./mole
H—H	104	C—N	73	C—Br	66
H—C	99	C=N	147	C—I	57
H—N	93	C≡N (HCN)	207	N—N	39
H—O	111	C≡N (RCN)	213	N=N	100
H—F	135	C—O	86	N≡N in N ₂	226
H—S	81 ^b	C=O (CO ₂)	192	N—O	48
H—Cl	103	C=O (CH ₂ O)	166	O—O	33 ^b
H—Br	88	C=O (RCHO)	176	(Peroxide)	
H—I	71	C=O (R ₂ CO)	179	Bonds in O ₂	118
C—C	83	C—F	105	F—F	37
C=C	146	C—S	62	Cl—Cl	58
C≡C (C ₂ H ₂)	194	C=S	114	Br—Br	46
C≡C (ave.)	200	C—Cl	79	I—I	36

^a T. L. Cottrell, *The Strengths of Chemical Bonds*, 2nd. Ed., Butterworth, London (1958).

^b L. Pauling, *The Nature of the Chemical Bond*, 3rd. Ed., Cornell University Press, Ithaca, N.Y. (1960).

(1) *Quantitative Treatment of Transition State.* In the transition state theory of reaction rates, the transition state is presumed to be a species with thermodynamic properties. It is further assumed that the transition state is in equilibrium with the reactants, whereupon a corresponding energy relationship can be written (eq. 21)

$$(21) \quad -\Delta F^\ddagger = T\Delta S^\ddagger - \Delta H^\ddagger$$

where \ddagger denotes the transition state, ΔF^\ddagger is the free energy of activation

(difference between energy of ground state or reactants and energy of transition state), ΔH^\ddagger is the heat of activation (nearly equal to the Arrhenius energy of activation, E_a described in §11-3B(3)), and ΔS^\ddagger is the entropy of activation. Activation is thus the process of going from ground state to transition state.

If the transition state for a simple reaction between A and B is denoted as AB^\ddagger , then the rate of the reaction is assumed to be proportional to the concentration of AB^\ddagger (experimentally it is proportional to the concentrations of A and B, as well). We therefore have the relationship of eq. (22)

$$(22) \quad \text{rate of reaction} = k[A][B] = C[AB^\ddagger]$$

where C is a derivable proportionality constant. From the assumed equilibrium $A + B \rightleftharpoons AB^\ddagger$ we get the relationship for its equilibrium constant

$$(23) \quad K^\ddagger = \frac{[AB^\ddagger]}{[A][B]}$$

and thus

$$(24) \quad k = \frac{C[AB^\ddagger]}{[A][B]} = CK^\ddagger$$

and

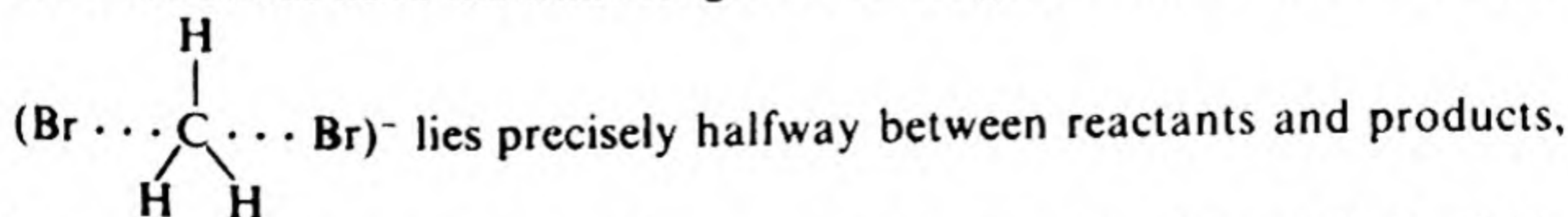
$$(25) \quad -\Delta F^\ddagger = 2.3 RT \log K^\ddagger = 2.3 RT \log k/C$$

From eq. (25), it may be noted that the more positive ΔF^\ddagger is, the smaller k is. For simple reactions, ΔH^\ddagger is always positive (k increases with increasing temperature). The larger ΔH^\ddagger is, the slower the reaction. ΔS^\ddagger may be positive (rate-enhancing) or negative (rate-retarding) depending upon whether or not the transition state is more restricted than the reactants.

A particularly simple reaction to formulate is the reaction of methyl bromide with radioactive bromide ion. Except for minor kinetic isotope effects (due to effects of mass differences) the forward and reverse reactions of eq. (26) are identical. The rate of the reaction may be followed



easily by noting how rapidly radioactivity is transferred into the alkyl bromide. In this case the transition state is symmetrical; both carbon-bromine bonds have the same length and strength, and the transition state



both of which have precisely the same energy content. Figure 11-3, which

describes a nonsymmetrical case (e.g., the reaction of methyl bromide with iodide ion), would have to be adjusted appropriately to accommodate the symmetrical case.

E. Consecutive Reactions

Thus far the discussions have been limited to simple reactions in which reactants proceed directly to products without the intervention of intermediates. While there are many examples of such paths, there are also many cases where one or more intermediates intervene. The intermediates may vary from relatively stable species, which can be isolated from the reaction mixture, to relatively unstable or reactive ones, where evidence for their existence may sometimes be obtained, but isolation is not possible. When an intermediate is involved in a reaction, there is a transition state lying at each free energy maximum between it and the reactants and between it and the products. A *stable intermediate* lies in a deep trough in the energy diagram (Fig. 11-8); a *reactive intermediate* lies in a

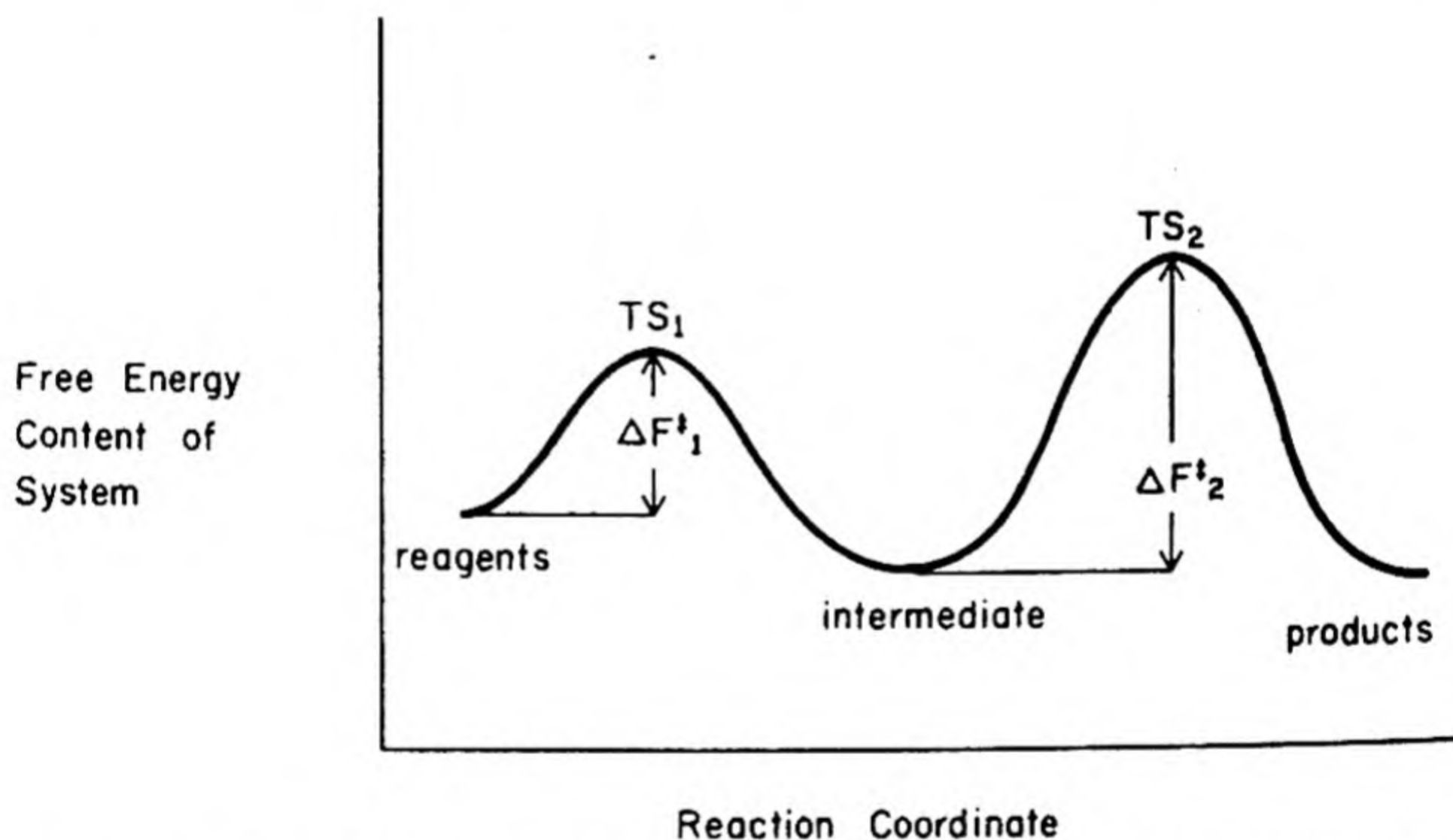


Fig. 11-8. Energy Diagram for a Two-Step Reaction with a Stable Intermediate.

shallow depression in the energy curve, (Fig. 11-9), and a transition state *always* lies at an energy maximum. One should note that multistep reactions are really series of single steps in which different transition states separate reactants and first intermediates, first intermediates and second intermediates, etc., and finally last intermediates and products.

Even when intermediates have too brief an existence to be isolated, it is often possible to get evidence of their existence and sometimes of their

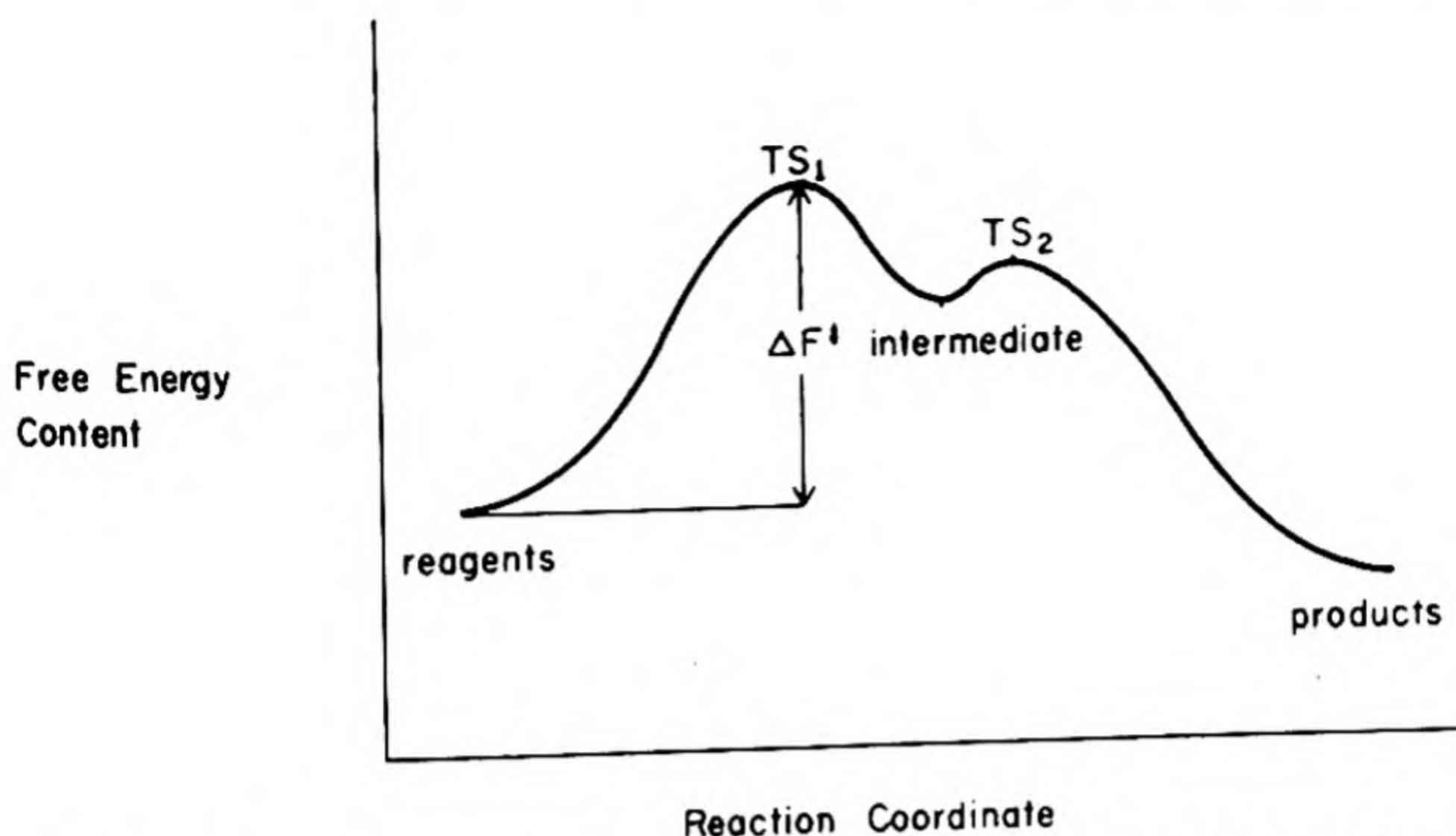
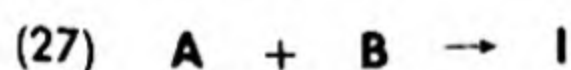


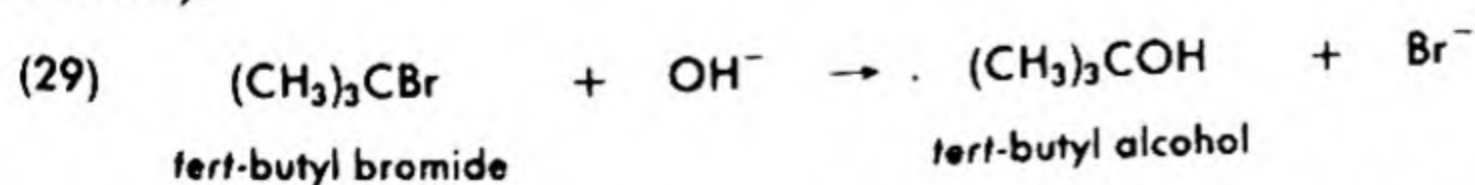
Fig. 11-9. Energy Diagram for a Reaction in Which the First Step is Rate-Determining.

properties by methods such as spectroscopy or reaction-rate studies, or by trapping them with substances with which they react very rapidly. When intermediates are involved in reactions, the overall rate equation is often more complicated than when there are no intermediates. In the reaction given in eqs. (27) and (28), where **A** and **B** are reactants, **I** is the intermediate and **C** the final product, it is possible, for example, for the rate of formation of **I** to be much slower than the rate at which **I** is transformed to **C** (Fig. 11-9).



Under such circumstances, the overall rate of reaction is approximately equal to the rate of formation of **I**. As **I** has a substantially lower energy barrier (Fig. 11-9) to cross to go to **C** than to return to reactants, substantially all of the **I** formed goes to products. ΔF^\ddagger for this situation is simply the ΔF^\ddagger for eq. (27), that is, to the *first* transition state.

An example of such a situation is observed in the dilute alkaline hydrolysis of *tert*-butyl bromide (shown in eq. (29) (see §12-1B(2) for details).



This is a two-step process in which the first step involves the heterolysis of the carbon-bromine bond to give a reactive carbonium-ion intermediate

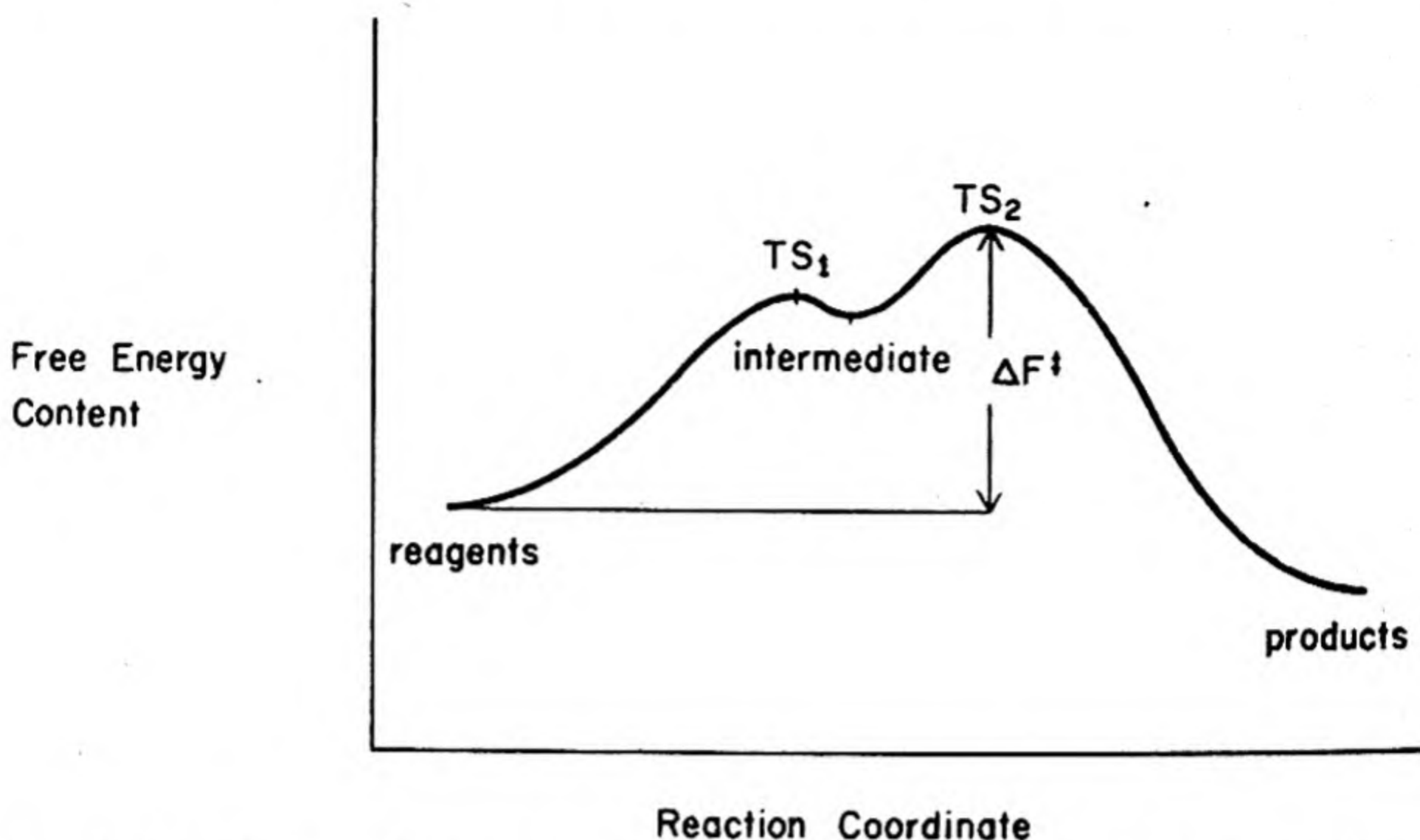
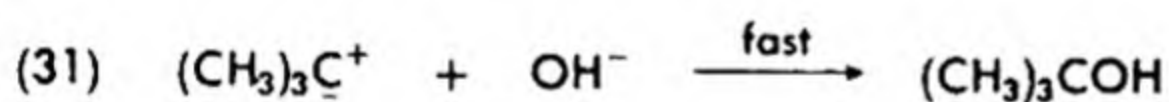
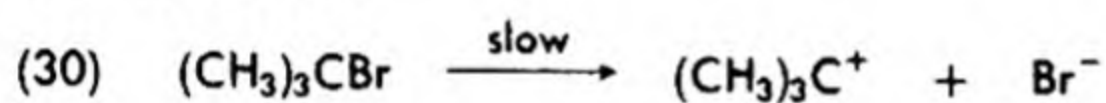


Fig. 11-10. Energy Diagram for a Reaction in Which the Second Step Is Rate-Determining.

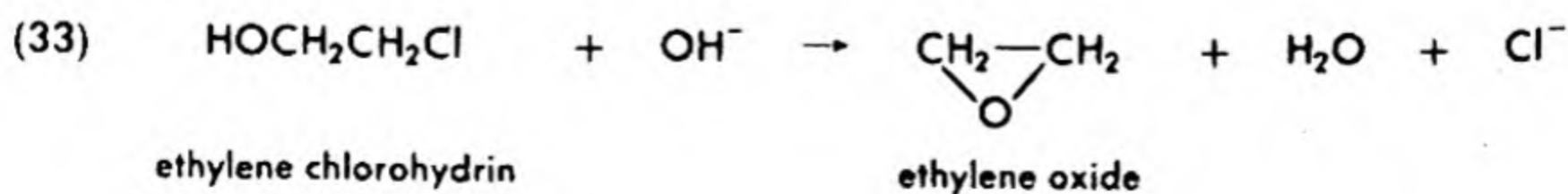
(eq. 30) and the second is the rapid coordination of that ion with hydroxide ion (or water, followed by neutralization) (eq. 31). The overall rate of the reaction thus depends on the rate of formation of the carbonium-ion intermediate.

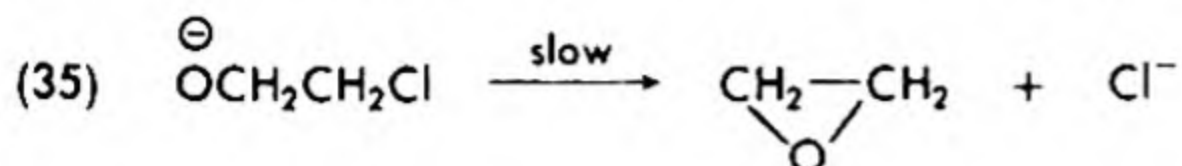
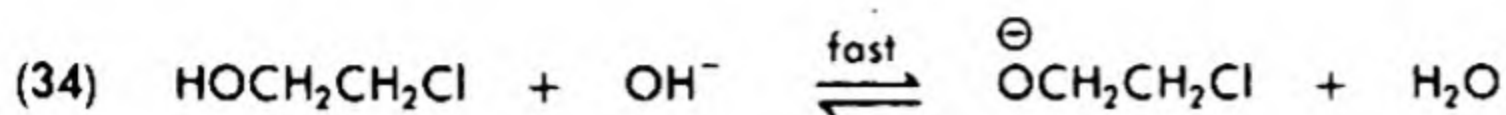


For an alternative reaction (Fig. 11-10), the intermediate, **I**, although still unstable with respect to **A** and **B**, has a lower energy barrier to cross to return to reactants than to go on to products. When these height differences are substantial, eq. (27) becomes an equilibrium (eq. 32), and the second step (eq. 28) becomes rate-determining. In such a case, ΔF^\ddagger is the barrier height from reactants to the *second* transition state.



An example of this type is the formation of epoxides from chlorohydrins with alkali (eq. 33). The first step (eq. 34) is a rapid and reversible acid-base proton transfer, while the second step is a slow one in which a carbon-oxygen bond is formed and a carbon-chlorine bond is broken (eq. 35).

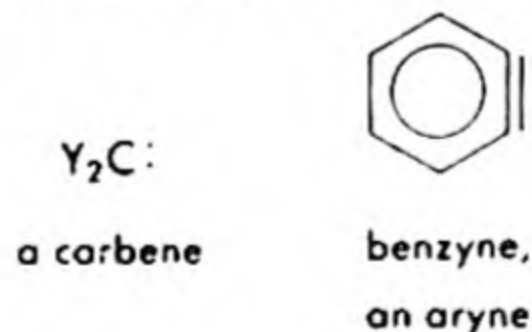




A slow step in a series of consecutive reactions is a bottleneck governing the rate of the whole series. Thus in the examples above, the first step (formation of the carbonium ion) is the *rate-determining step* in the hydrolysis of *tert*-butyl bromide, while the second step is the *rate-determining step* in the ethylene oxide formation. The idea of the *rate-determining step* in multistage reactions is one much used in studies in organic chemistry. Many apparently simple reactions have a number of steps, of which one or more is relatively slow and therefore termed rate-determining.

11-4 TYPES OF REACTIVE INTERMEDIATES

The transition states near to reactive intermediates (Figs. 11-9 and 11-10) resemble closely the intermediates themselves, hence information about the intermediates is very helpful to understanding the reactions. Several types of reactive intermediates have been recognized as participants in organic reactions, including, among others, carbonium ions, free radicals, carbanions, carbenes, and arynes. These will be treated in detail in later chapters. However, a look at the first three of these may be helpful here. A carbonium ion, Y_3C^+ , contains a carbon atom which has only six electrons in its valence shell and which has a positive charge. A carbon free radical, Y_3C^\cdot , contains a carbon atom which has seven electrons in its valence shell. The high reactivities of carbonium ions and carbon free radicals are caused by the necessity of the carbon atom to complete its octet. A carbanion, Y_3C^- , has an unshared electron pair and a negative charge on a carbon atom. Its high reactivity is due to its strong basicity and nucleophilicity (see below).



11-5 TYPES OF IONIC REAGENTS; ELECTROPHILES AND NUCLEOPHILES

For those reactions which have been designated heterolytic or ionic—that is, for electron pair reactions—it is clear that one of the reagents is the electron-pair donor and the other the electron-pair acceptor. It is thus

apparent that the Lewis acid-base theory applies specifically and generally to this type of reaction. The electron pair acceptor is called an *electrophile* or *electrophilic reagent* and is more reactive the greater the tendency to gain an electron pair. These reagents (which may also be termed Lewis acids) must either have an empty or potentially empty orbital which can accept the electron pair or lose a group with an electron pair in the course of reaction.

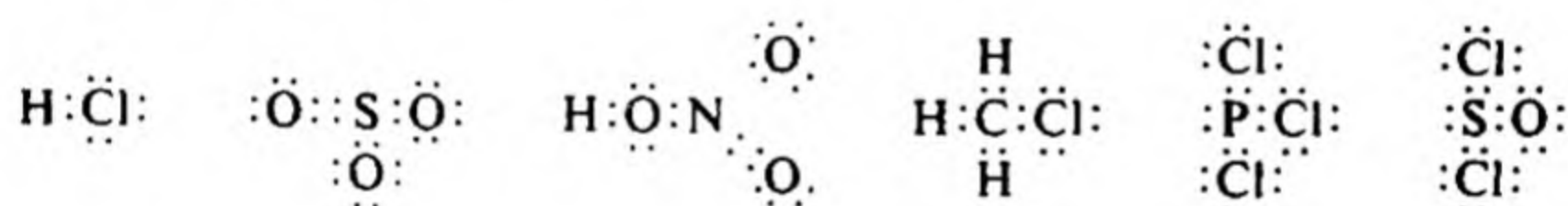
An electron-pair donor is termed a *nucleophile* or *nucleophilic reagent* (also Lewis base), for it seeks an atomic nucleus with which to share its

TABLE 11-3. Typical Electrophiles

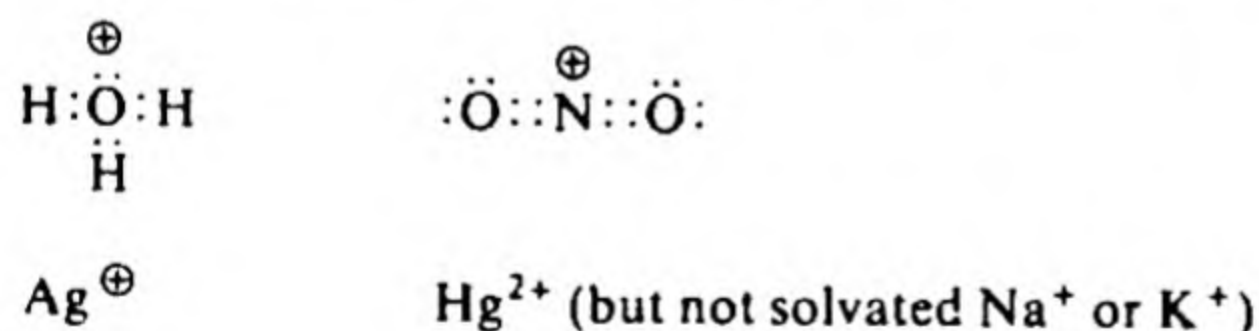
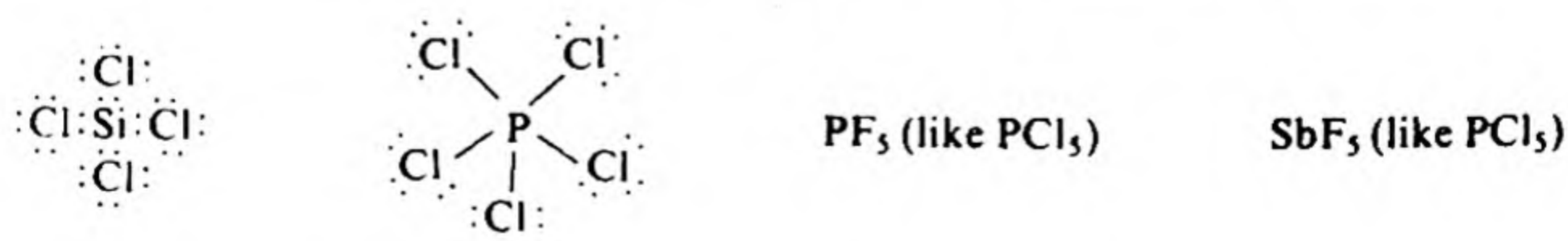
Compounds Containing Electron-Deficient Atoms



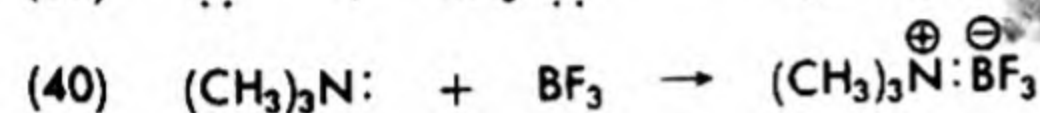
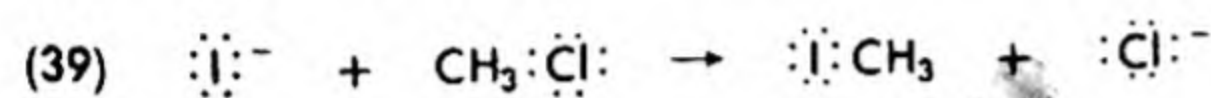
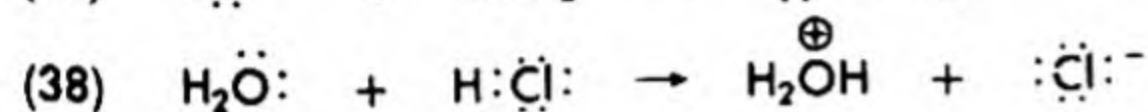
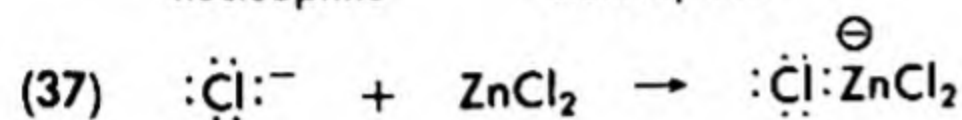
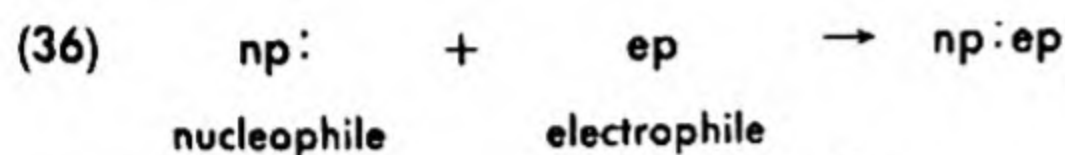
Compounds Containing Elements or Groups in Covalent State Which Are More Stable as Negative Ions, or Which Have a High Concentration of Electronegative Elements



Nonmetallic Positive Ions and Certain Metal Ions

Compounds of Elements Which Can Accept Electron Pairs into *d* Orbitals

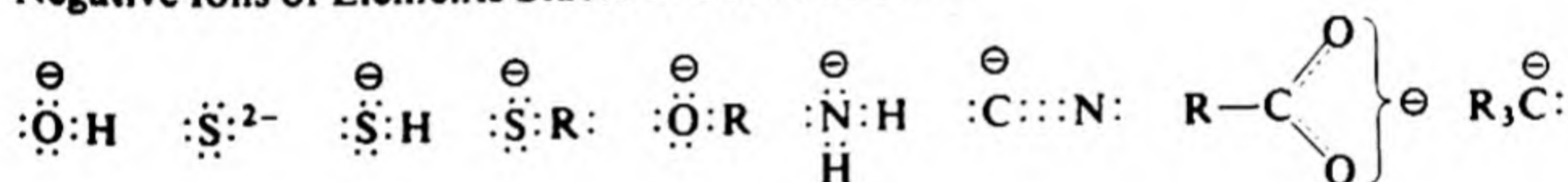
electron pair. It should be apparent that these two reagent types meet each other's electronic demands—that is, nucleophilic reagents react with electrophilic reagents. Some of these are exemplified in eqs. (36) through (40) and Tables 11-3 and 11-4. It is perhaps needless to state that substances vary substantially in their strengths as nucleophiles or as electrophiles.



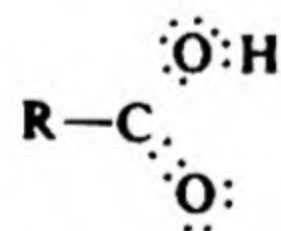
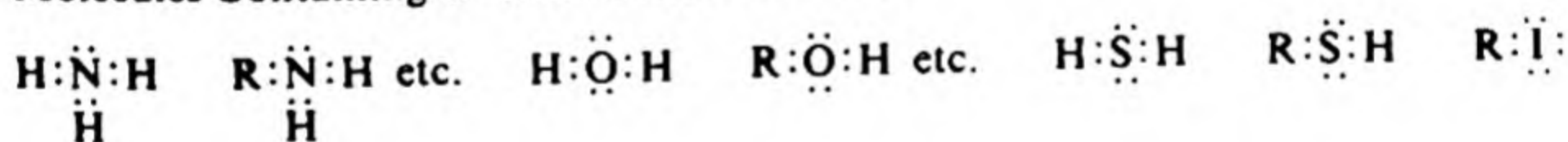
Chemists are now attempting to derive a general theory of nucleophilicity (strength of a nucleophile) and electrophilicity.

TABLE 11-4. Typical Nucleophiles

Negative Ions of Elements Stable in Covalent State



Molecules Containing Unshared Electron Pairs



Molecules Which Contain Pi Orbitals on Relatively Electropositive Atoms



11-6 STERIC FACTORS; MOLECULAR GEOMETRY

A. Steric Hindrance

For reagent particles to interact, their active centers must be able to touch; indeed, the groups present in whatever transition state is formed must not be too crowded, or the transition state will be so difficult to form that reaction will occur only very slowly. Although there is a certain amount of flexibility in molecules, as exemplified by abnormal bond angles due to repulsive forces (Fig. 11-11), bulky groups can place severe restrictions on the formation of transition states (Fig. 11-12). Such slowing or preventing of reaction due to spatial interference of groups is termed *steric hindrance*, one of several primary *steric effects*, and is noted when there is severe crowding of groups in the transition state as compared with reagents.

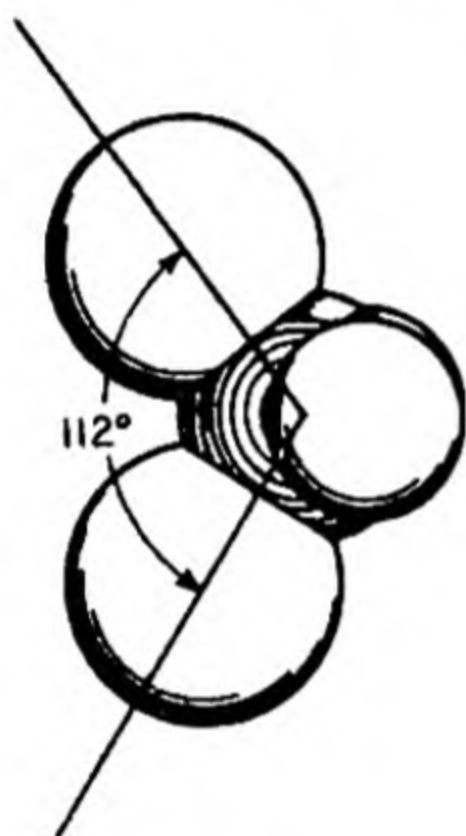
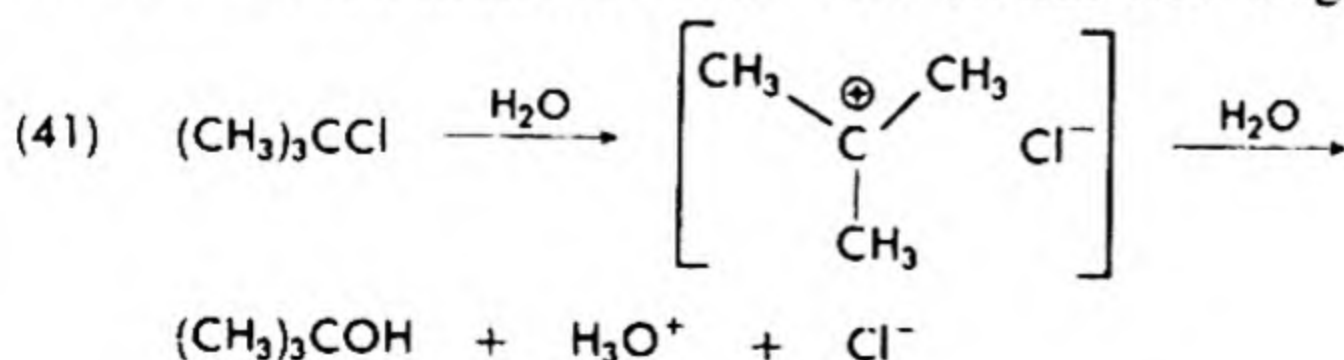


Fig. 11-11. Abnormal Bond Angle in Dichloromethane Due to Charge Repulsions (or Alternatively, Due to Unequal Hybridization of sp^3 Orbitals).

B. Steric Acceleration

On the other hand, certain types of transition states have less crowding than the reagents. Such a situation leads to steric relief, or decrease of crowdedness, when the transition state is formed, and may involve sensational increase in reaction rates when bulky groups are present. This phenomenon is termed *steric assistance* or *steric acceleration*. For example, the reaction-rate constant for eq. (42) is 40,000 times that for eq. (41). In these reactions, the rate-determining step involves the formation of a carbonium-ion intermediate. This ion has 120° angles between the groups



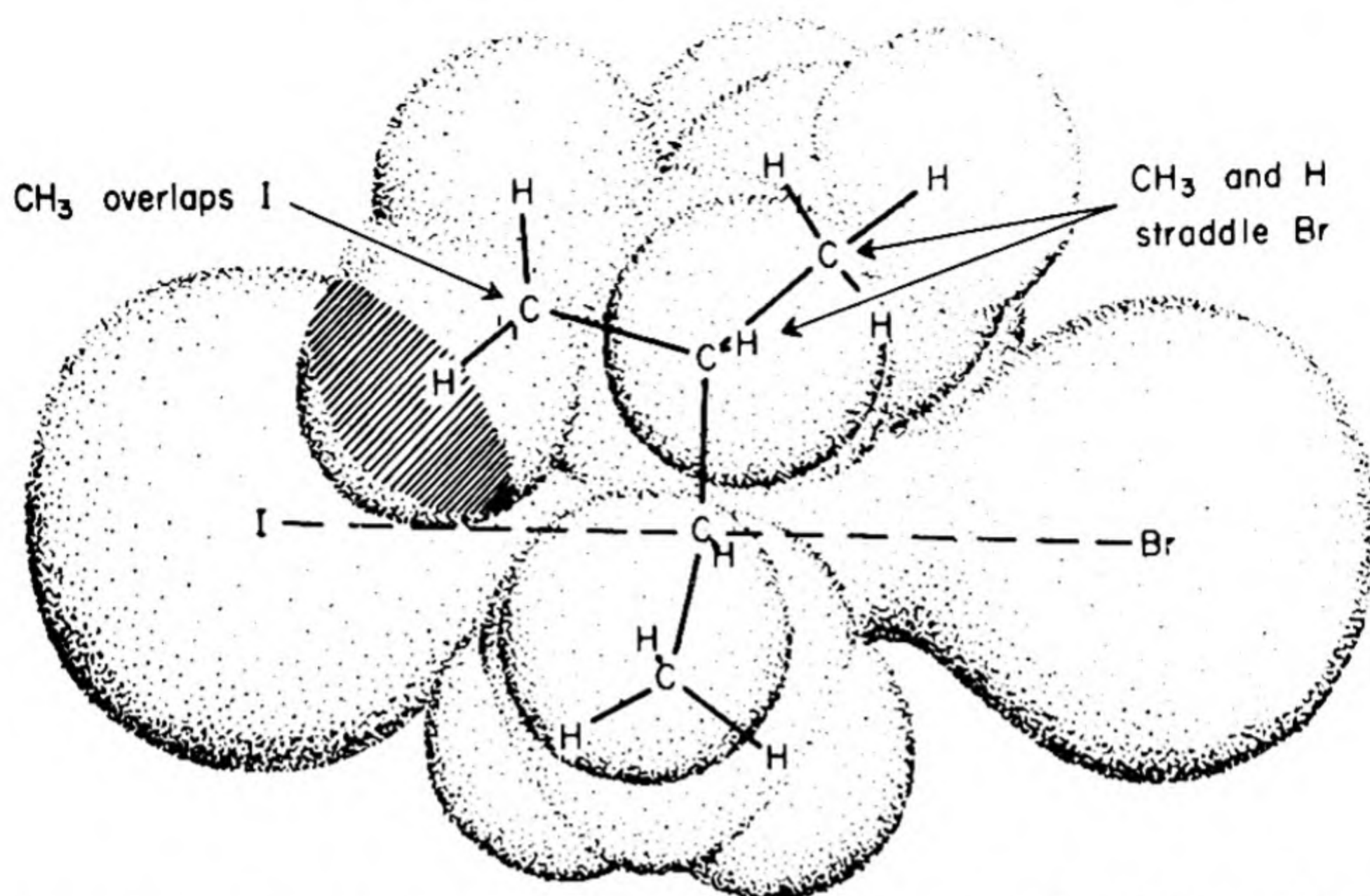
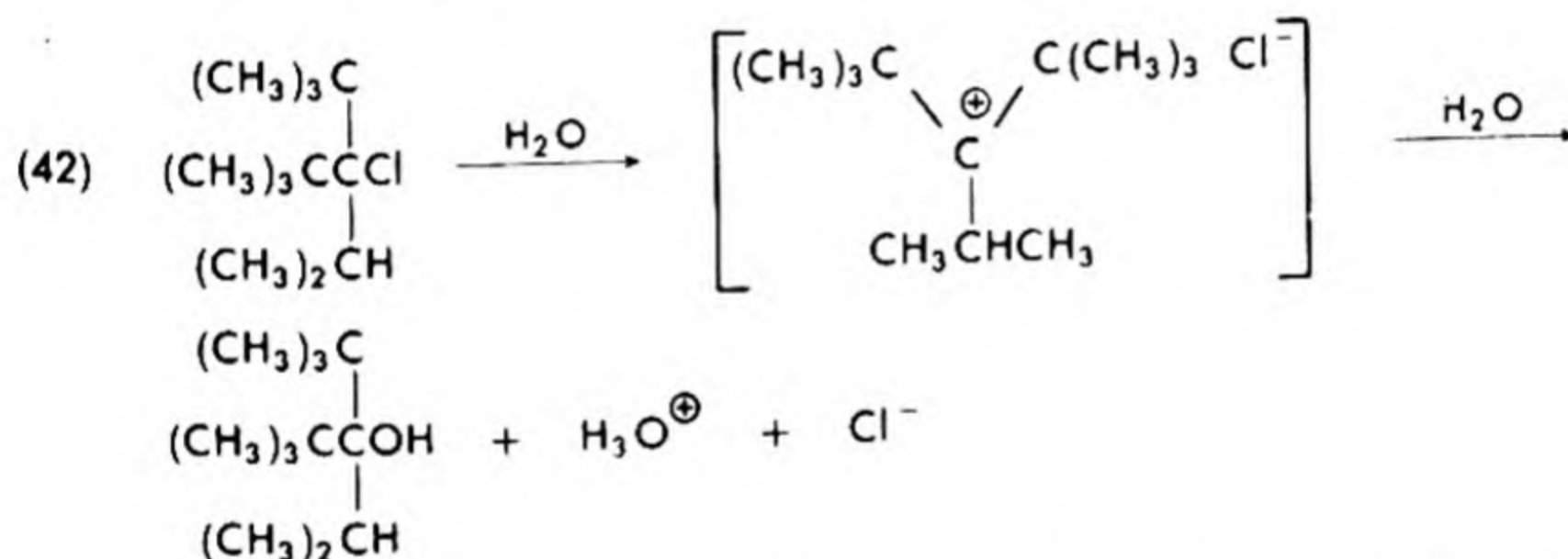


Fig. 11-12. Crowding in One Conformation of a Transition State During a Hindered Displacement of Bromide by Iodide in 2-Bromo-3-methylbutane.



on the cationic carbon, while the initial halide had tetrahedral carbon, with angles of nearly 109.5° . The transition state therefore has more room between groups than the reactant. Since this is more important with large groups than with small ones, steric acceleration is observed.

C. Conformational Effects and Stereospecificity

Steric effects also involve restricted rotation of groups about bonds. While rotation does occur about single bonds in open chain compounds, §5-1B, even in ethane it is not completely free (Figs. 11-13A and 11-14). Particular conformations are favored, especially when large groups or atoms with charge repulsions are involved, such as 1,2-dichloroethane (Figs. 11-13B and 11-15).

Certain reactions are stereospecific, which means that entering or leaving groups must have certain spatial relationships to each other (e.g.,

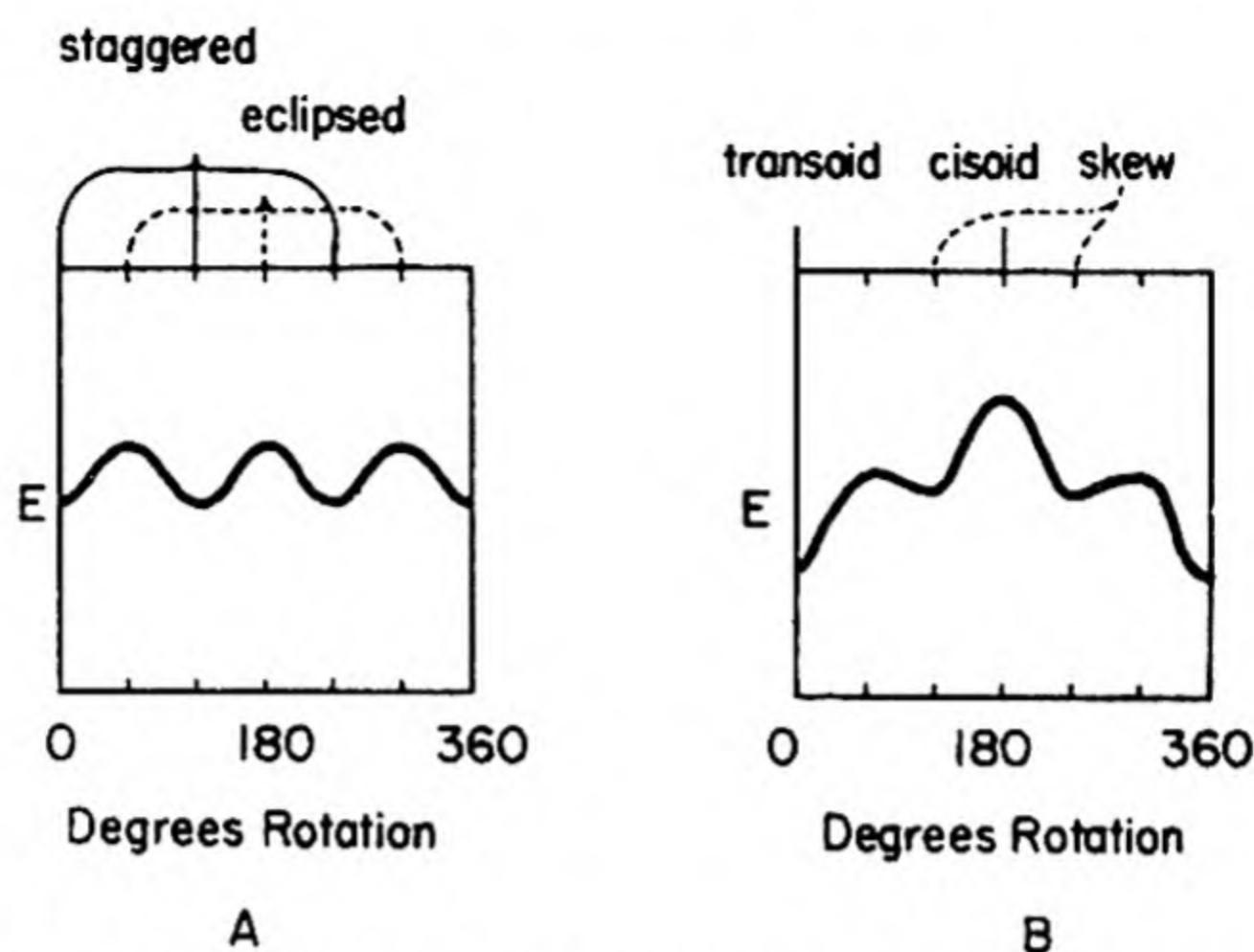


Fig. 11-13. Potential Energy of Molecules as Function of Angle of Rotation. (A) Ethane, (B) 1,2-Dichloroethane.

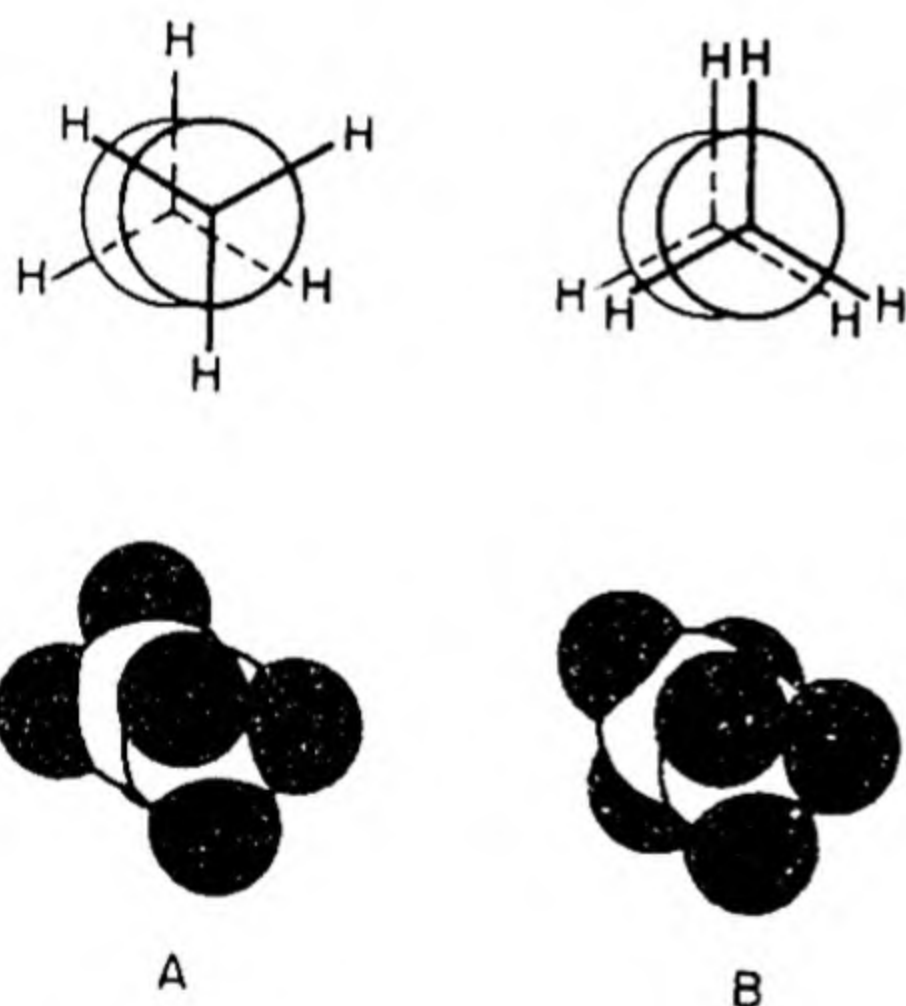
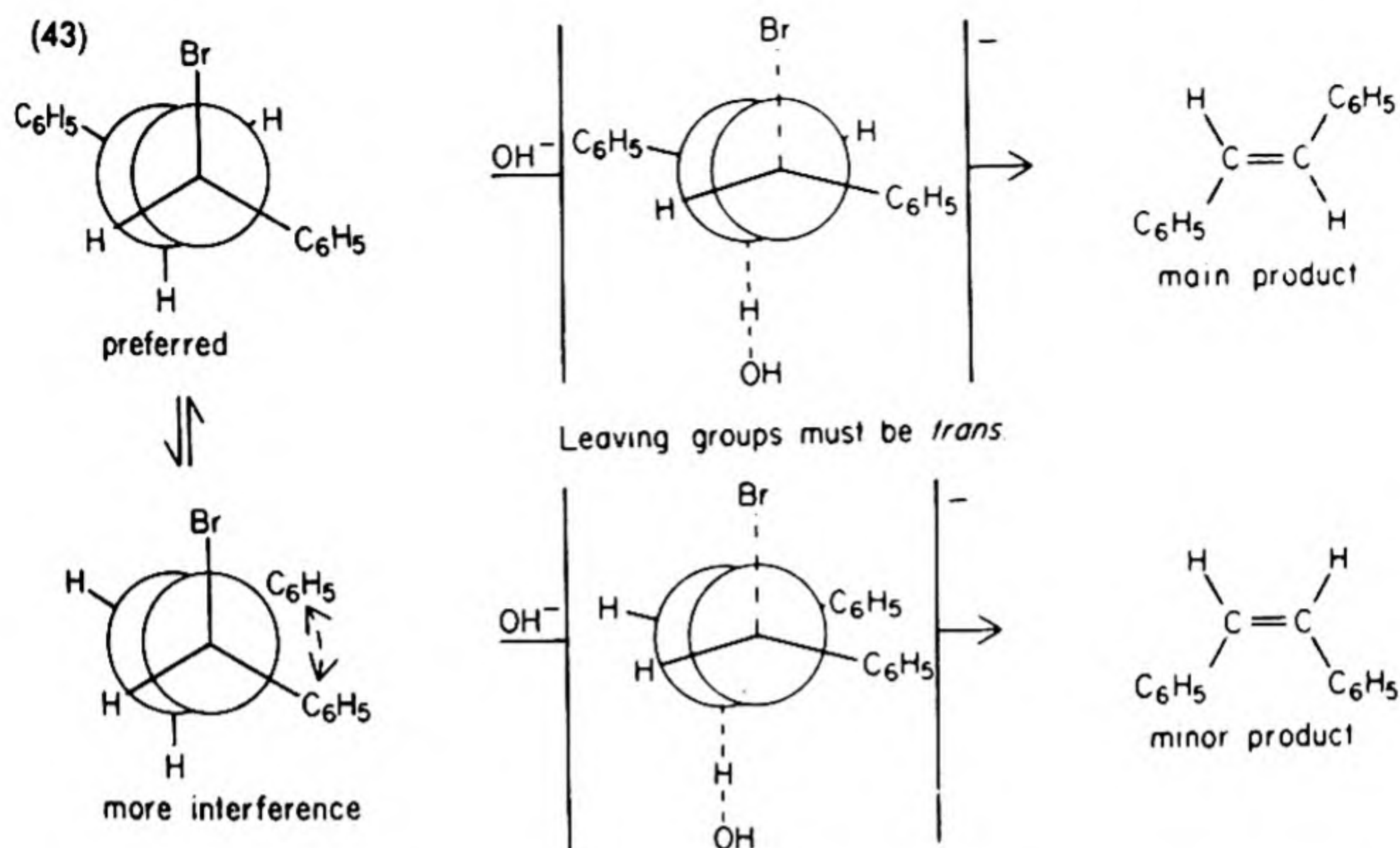


Fig. 11-14. Conformations of Ethane. (A) Staggered, (B) Eclipsed.

outline 43). For such reactions, preferred conformations in the transition state can control the rate and sometimes the course of the reaction.

D. Configuration and Intramolecular Reactions

Orbital p - p pairing to form π bonds usually completely restricts rotation at 20° . The energy barrier, often in the neighborhood of 40–50 kcal./mole (Fig. 11-16), between the *cis* and *trans* isomers can usually be crossed only at relatively high temperatures, or when energy is added by absorption of light.



Cis and *trans* isomers are not necessarily of equal energy; if the molecules are given enough energy to pass over the potential barrier, they usually form an equilibrium mixture favoring the *trans* isomer. The difference in energy, ΔF , between the *cis* and *trans* forms (Fig. 11-16B), determines the point of equilibrium.

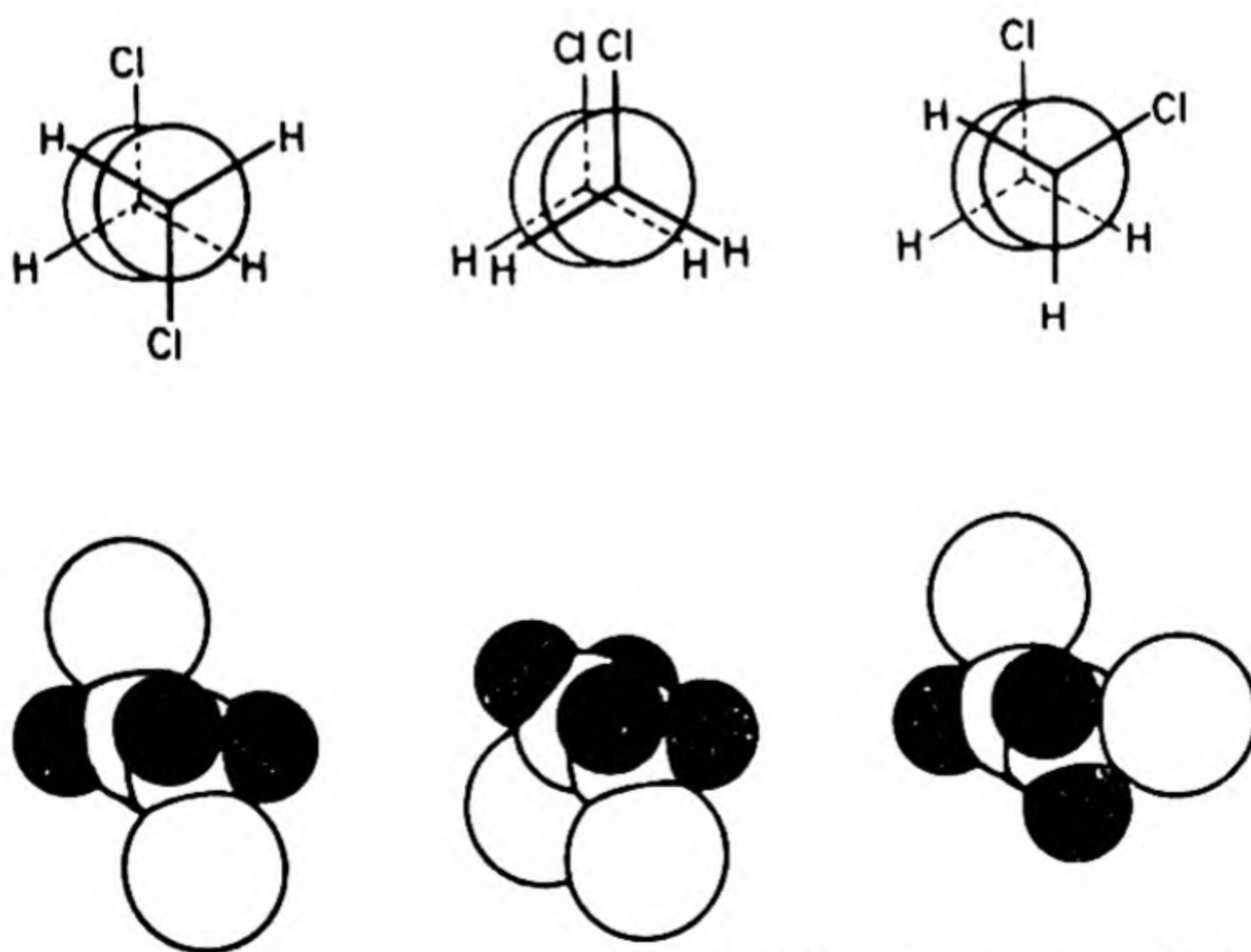


Fig. 11-15. Conformations of 1,2-Dichloroethane. (A) Staggered (transoid), (B) Eclipsed (cisoid), (C) Skew (gauche).

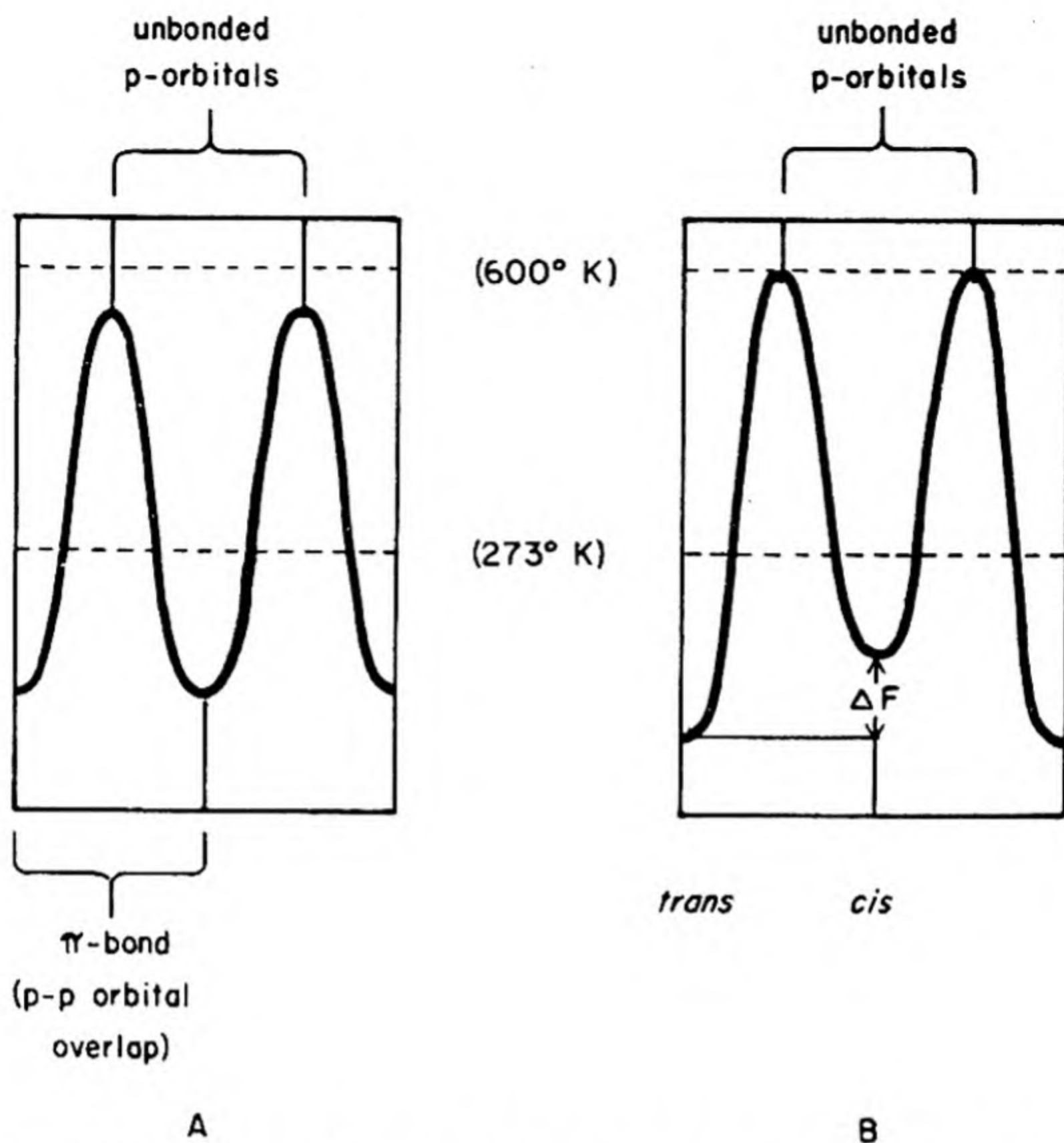
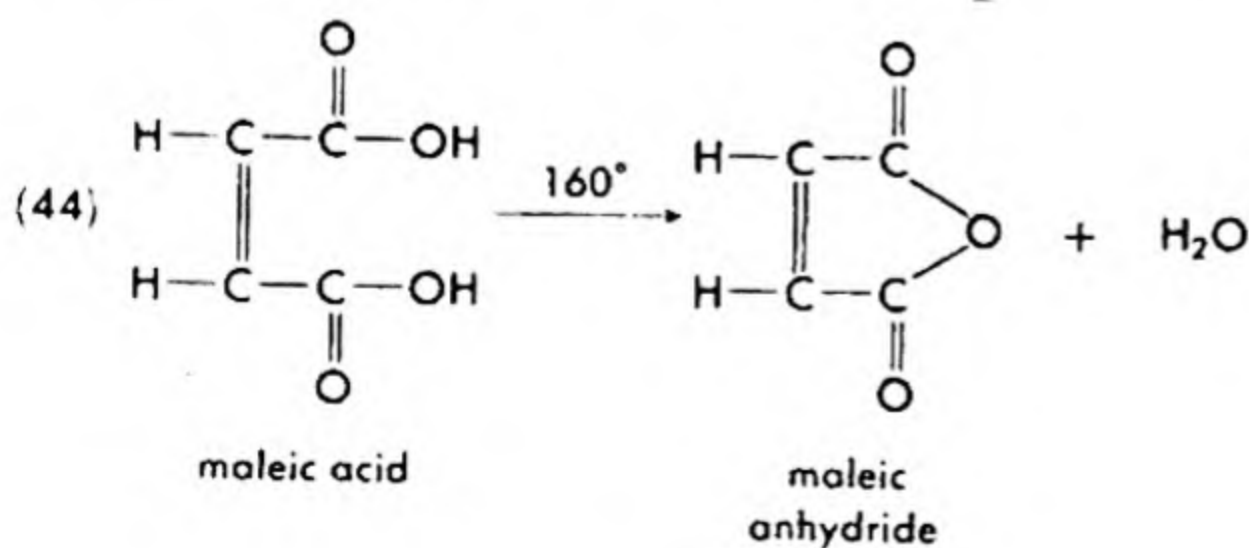
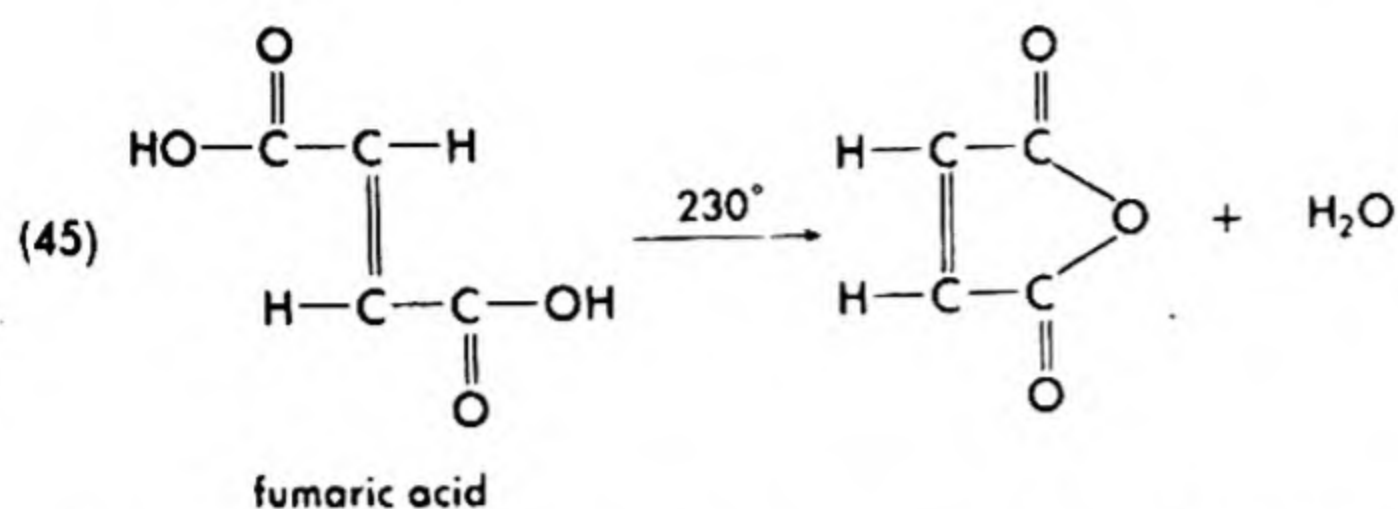


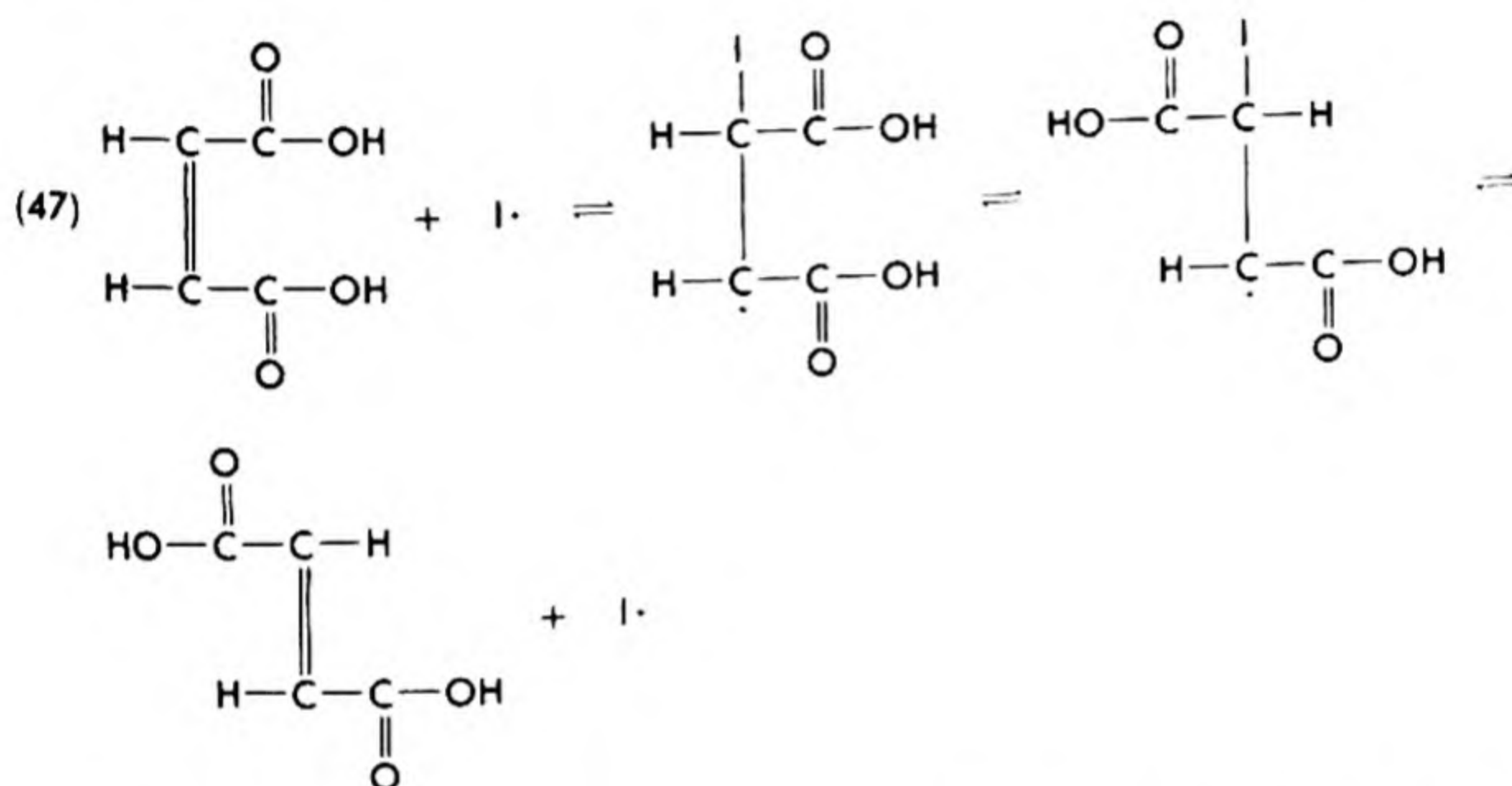
Fig. 11-16. Energy Barriers to Rotation in Double Bonds. (A) Ethylene, (B) 2-Butene.

In cyclization reactions the importance of geometric factors is quite obvious. Maleic and fumaric acids, which are *cis-trans* isomers, perform invaluable roles as reference compounds for establishment of configurations of all *cis-trans* isomers. Maleic acid (*cis*-butenedioic acid) is very readily converted to a cyclic anhydride (eq. 44), while fumaric acid is not. When very strongly heated (eq. 45), fumaric acid forms maleic anhydride, but must change configuration to do so.





Iodine lowers the potential energy barrier between *cis* and *trans* isomers by temporary formation of an unstable, free-rotating radical (eqs. 46 and 47).



The greater stability of the *trans* form in those isomers of which the configuration has been unequivocally established is the general rule, although there are a number of exceptions. Also, the *trans* isomer more often has the higher melting point. These facts have been used as guides in assigning tentative configurations before unequivocal proof.

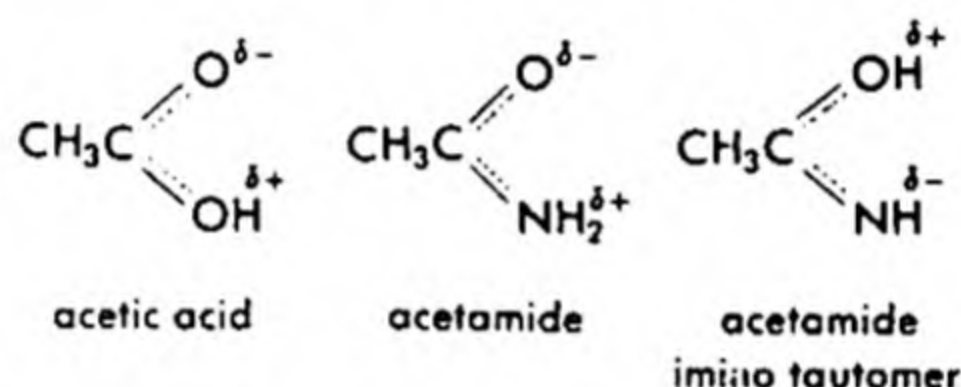
Reliable configurations can be established only in cases where cyclization is possible, or where the isomers can be related by mild chemical transformations to reference compounds such as the butenedioic acids. Infrared and nuclear magnetic resonance spectra have provided indirect methods of assigning configuration which are quite reliable.

11-7 RESONANCE IN CONJUGATED SYSTEMS

Resonance which *delocalizes* p electrons with little effect on the charge distribution in a molecule or ion contributes largely to the stability of the

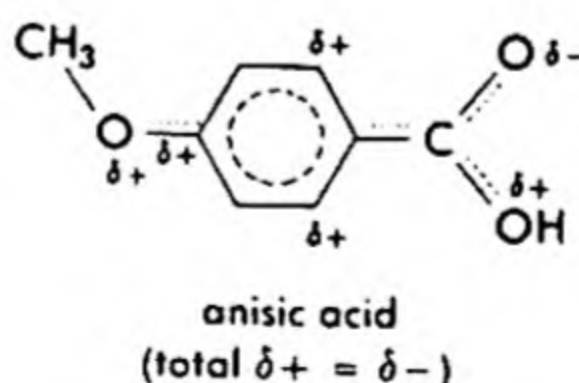
molecule or ion. Thus, the resonance energies of aromatic hydrocarbons are relatively large: benzene, 36 kcal./mole; naphthalene, 61 kcal./mole; anthracene, 84 kcal./mole. Delocalization of a charge likewise contributes greatly to stability. Acetate ion, guanidinium ion, $C(NH_2)_3^+$ and the allyl cation $CH(CH_2)_2^+$ are examples in which resonance stability contributes to acid strength of acetic acid (§7-3A(2)), base strength of guanidine (§10-3B), and ease of nucleophilic displacement in allyl halides (§12-1B(4)).

Resonance which involves *charge separation* contributes relatively less to stability of a molecule or ion, unless large electronegativity differences between the atoms which bear portions of opposite charge are in the direction to favor the charge separation. Thus, acetic acid has 15 kcal./mole of resonance energy; acetamide has 25 kcal./mole and the less stable tautomeric form of acetamide has electronegativity differences in the wrong direction. The esters of the imino tautomer, called alkyl

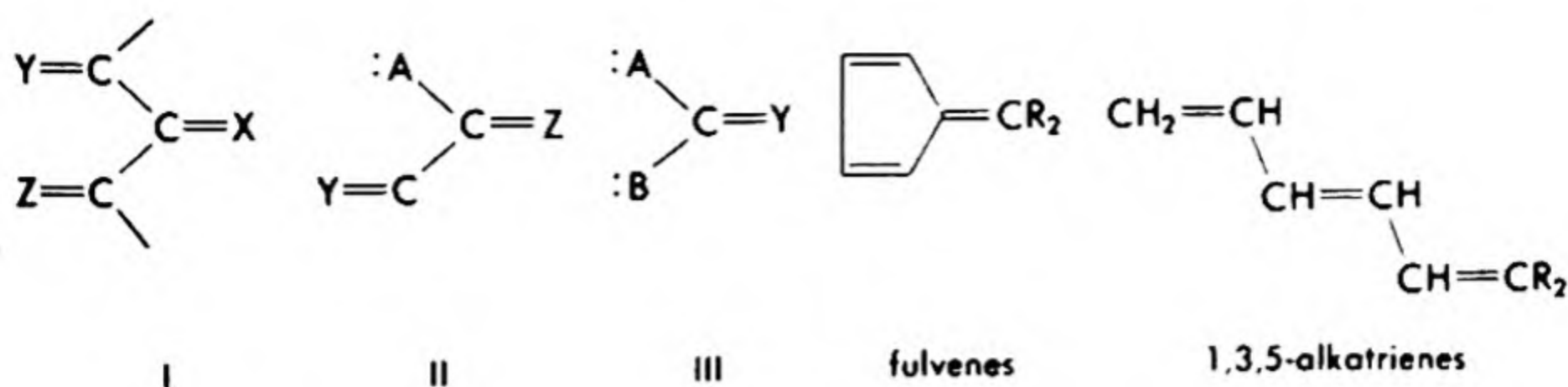


acetimidates or alkyl iminoethyl ethers, are correspondingly highly reactive.

When charge separation is in the direction to place one of the charges near another locus of charge of like sign, the contribution of such resonance to the stability of the ion is negligible. This was already cited as a contributing factor in the low acid strength of anisic acid (§10-2E). On the other hand, when one of the charges in the resonance-stabilized polar molecule is delocalized, such resonance is more important to stability than when neither charge is appreciably delocalized. Thus, anisic acid (§10-2E) is more stable than acetic acid because the positive charge is extensively delocalized in the former.



Cross-conjugated systems (I through III) have lower resonance energies than comparable linear or closed systems. Thus, fulvenes have 2 kcal./mole of resonance energy less than 1,3,5-alkatrienes and about $\frac{1}{3}$ of the resonance energy of benzene.



The effects of resonance on chemical reactions (equilibrium and reactivity) are profound and in many cases predictable. In equilibrium situations, any change which increases resonance stabilization in products more than in reactants shifts the equilibrium toward products. The converse is also true. In reactivity considerations, resonance effects on transition states and on reactants are considered. If changes in substrate increase resonance stabilization of the transition state more than reactants, the reaction rate is increased. If reactants are stabilized by changes more than the transition state, the rate is decreased.

11-8 CATALYSIS

It was noted that the rate of a reaction depends upon the height of the free energy barrier, ΔF^\ddagger . The number of molecules crossing the barrier per unit of time can be increased by raising the temperature. This is often done by conducting reactions at the refluxing temperature of the solvent. Temperatures higher than this can be reached by conducting the reaction under pressure in an autoclave or in a sealed tube, but such devices have limitations. In addition, raising the temperature may cause competing reactions of reactants, of intermediates, or of products to intervene so that utilization of the reaction may be unsuccessful.

An alternative procedure for increasing the rate of a reaction is to find a new pathway with a lower ΔF^\ddagger . This is the function of a catalyst. A catalyst modifies the reaction course in such a way that the new transition state containing the catalyst is lower in energy than the unmodified one. A catalyst thus operates by involving itself with reactants in the rate-determining step or in a step preceding the rate-determining step, so that it is present in the rate-determining transition state and can stabilize it. The catalyst then dissociates itself from the products and is thus regenerated for subsequent use by other molecules. For practical reasons, it is necessary that the catalyst does not accelerate competing reactions to the same extent as the desired reaction.

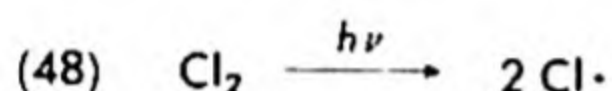
Catalysts function in various ways. Solid catalysts often provide active sites on which reactions may occur; these may be, for example, acid sites where acid-base reactions take place or sites where hydrogen molecules are dissociated in hydrogenation-dehydrogenation catalysts. Such cata-

lysts are adsorptive materials, and molecules must be adsorbed to become activated.

In a chemical equilibrium a catalyst cannot change the equilibrium constant, since to do so would be to do work on the reaction in violation of the principle of conservation of energy. Thus, a catalyst must affect the rates of the forward and reverse reactions proportionately. There are many cases in which the catalyst for certain steps in an overall reaction is consumed in later steps as a reactant, so that the foregoing statements have certain readily understandable exceptions.

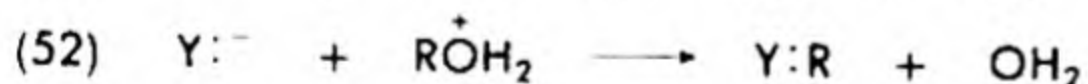
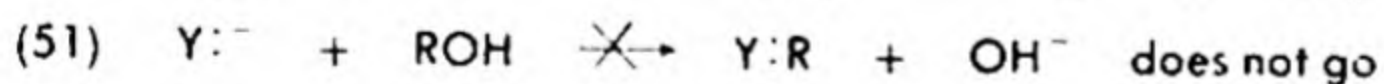
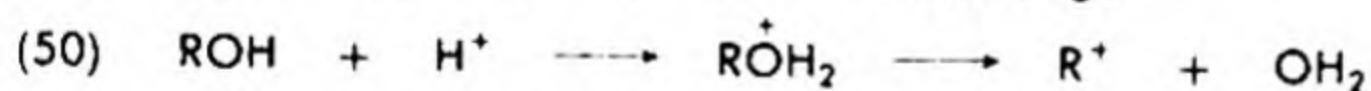
The many specific catalysts for specific reactions are noted in appropriate sections of this text.

Activation by light (sometimes erroneously called catalysis) involves the dissociation of molecules into free radicals (photolysis), an example of which is given in eq. (48). These radicals may initiate chain reactions (§15-2). A photon of light ($h\nu$) is consumed for each molecule dissociated.



A. Acid and Base Catalysis

Among the most common catalysts for organic reactions are acids of both the protonic and the Lewis type. The dissociation of an alcohol into a carbonium ion and hydroxide ion (eq. 49) does not proceed at an appreciable rate, while the acid-catalyzed reaction (eq. 50) goes readily in many cases. In addition, direct displacement of hydroxide from an alcohol by a nucleophile does not occur (eq. 51). Again acid catalysis makes such a reaction possible (eq. 52). The cleavage of carbon-oxygen bonds is, in general, subject to acid catalysis, as are many other reactions.



Many reactions have their rates increased by bases and are therefore base-catalyzed. These bases follow one of the paths described above for the action of catalysts and may therefore properly be called catalysts. However, in the course of many base-catalyzed reactions, acid species are formed, which of course consume base so that the base is involved in the stoichiometry of the reaction. Some chemists prefer to call such reactions base-promoted reactions.

B. Solvent Effects

The vast majority of inorganic reactions occur in water as solvent. In this situation, solvent effects are comparable, hence can be neglected,

especially for dilute solutions in which the concentration of the solvent is virtually constant. Organic reactions, however, are of necessity carried out in a variety of different solvents. The polarity, polarizability, and hydrogen-bonding ability of the solvent have important influences on the rate, and often the character, of the reaction. The chemical nature of the solvent (acidity, basicity, etc.) is also important. In general, when the transition state for a reaction is more polar than the reactants, the reaction is accelerated by highly polar solvents, as the polar solvent tends to stabilize the more polar state to a greater degree. For the same reason, reactions involving dispersion or loss of charges in the transition state are favored by nonpolar solvents (see Fig. 11-7). Free radical reactions are little influenced by the polarity of solvent, but can be influenced to some degree by any radical-stabilizing effects of solvents.

In most of the reactions discussed in this text, it will be assumed that ionic reagents are dissociated into their free ions. This assumption is often not true, as, in solvents of low dielectric constants, such reagents in fact exist as ion pairs or ion aggregates. Changes in solvents from one of low dielectric constant to one of high dielectric constant may have significant effects on reactivity. In addition, certain solvents have remarkable affinities for cations and low affinities for anions. Such solvents, in which anions are substantially bare, increase the reactivity of these anions as nucleophiles or as bases by factors often exceeding 10^6 over corresponding reactions in water where the anions are strongly solvated.

11-9 PRINCIPLES OF SYNTHESIS

A. Synthesis Economics

Three primary considerations in the choice of a path to a desired compound are the overall yield, the cost of materials, and the length of time required for the synthesis.

The overall yield of a product is the yield over the several steps from the first reagents to the desired products. Human effort, utilized reagents, equipment, and power are wasted unless a gratifying quantity of the product is obtainable. In working synthesis problems, we must keep in mind that only bona fide reactions, preferably those which give high yields, are acceptable. Not all reactions that look good on paper yield to practice. There is no place for fairy tales; the yield for an impossible reaction is zero (as is also the grade for an answer including impossible steps).

Process cost can be a factor in both laboratory syntheses and industrial processes. Reactions requiring heavy equipment or tricky separations are usually confined to industrial processes, where the savings in time and manpower often offset heavy equipment expenditures. On the other hand,

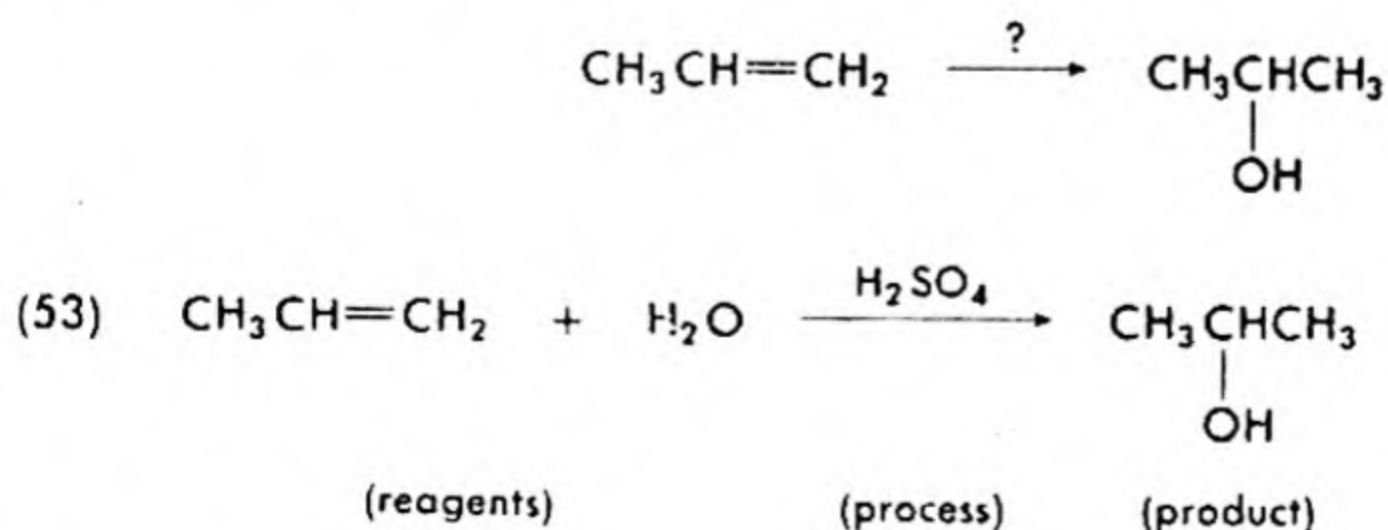
industrial processes are especially sensitive to the cost of raw materials, since the books must show a profit from the sale of products. The research chemists may often use a more expensive chemical to save time or equipment, but his budget is not unlimited either.

Time is of value to both the industrialist and the researcher. However, the industrialist can increase output simply by increasing the scale of operations, which makes practical many cyclic processes based on partial conversions. The researcher, on the other hand, must depend on a batch process in limited equipment, hence on reactions of high yield whose products are readily separable from the by-products. In general, the more steps in a synthesis, the longer is the time consumed and the lower the yield. However, a specific case may dictate a longer route due to lower yields of individual reactions in a shorter pathway to a given product. In problem solving, we look for methods specially fitted for the conversions desired, so as to minimize the number of steps.

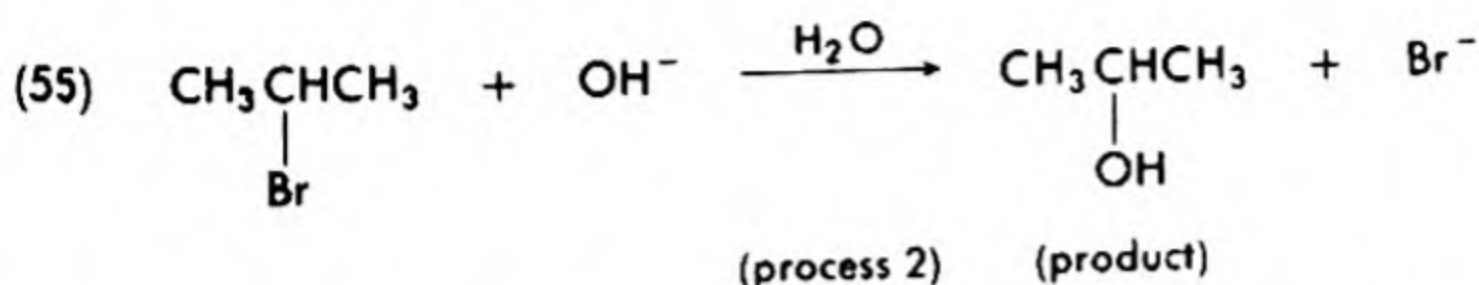
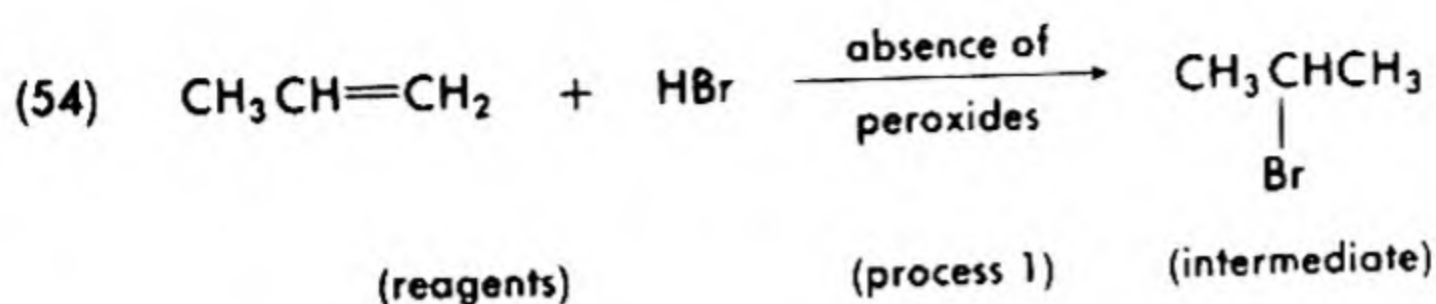
Industrially, by-products from a synthesis can be an asset, if they are useful and readily and cheaply recovered, or a liability, if they become a waste to be disposed. By-products produced through side reactions (reactions competing with those used to make the desired product) are inevitably a liability since their production decreases the yield of the more desirable product. This is particularly true in the laboratory, where only the desired product has any value.

B. Reaction Fitting

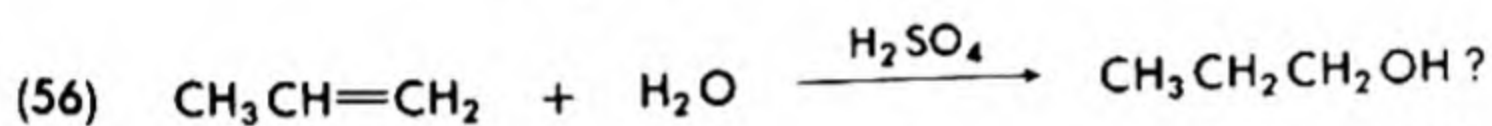
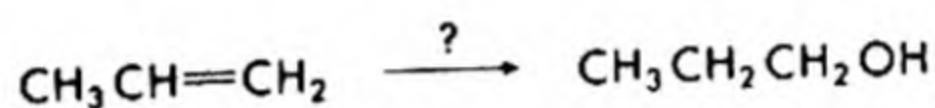
It should be apparent that no gaps can occur in a sequence of reactions in a synthesis. Available to each step in the synthesis are only those products made by preceding reactions in the sequence. Usually the ready availability of inorganic reagents is assumed, simply because the problem is an exercise in organic chemistry, not inorganic chemistry. However, if a product is truly made from a given starting material, there must be a continuous link of processes and intermediates from the raw material to the product. A reaction or sequence of reactions must be chosen exactly to fit the starting material to the product thus:



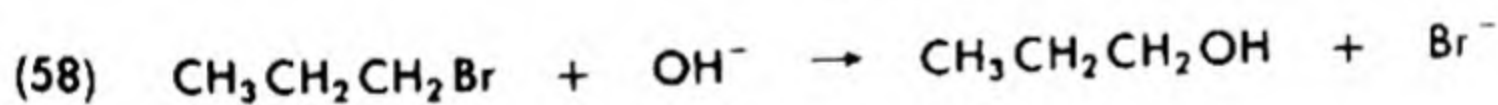
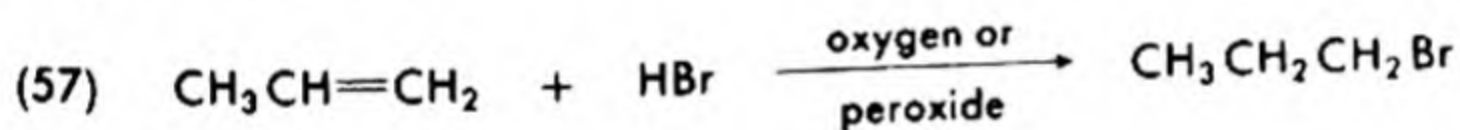
Other processes might be considered.



The yield by the one-step method is better than that by the two-step method. Furthermore, the sulfuric acid (only a catalyst, hence reusable) is much cheaper than the expendable hydrogen bromide and sodium hydroxide. But the types of reactions in the two-step process should not be cast aside as worthless; instances occur which can be solved best by just such a process:

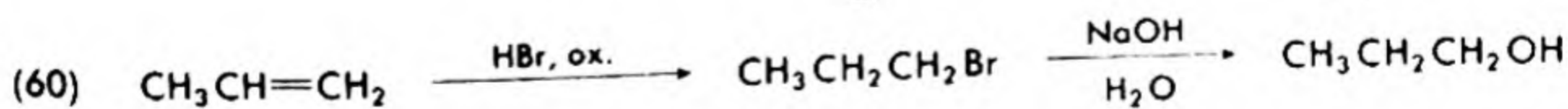
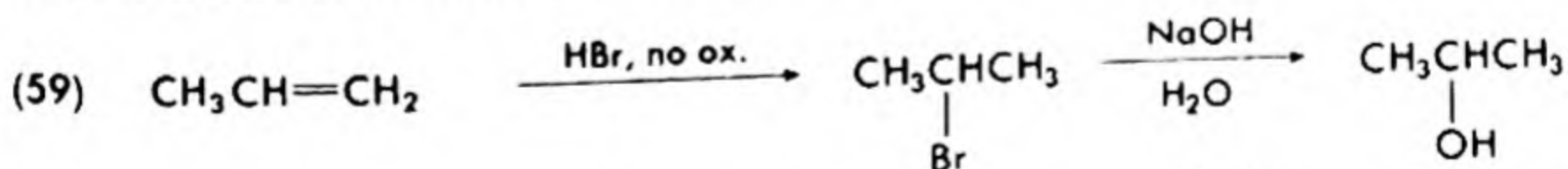


But no, this reaction is by present knowledge impossible (Markovnikoff's rule, §14-2B), so it may not be proposed. In this case, only the longer way is acceptable.



C. Economy in Time and Space for Students Too

By the time a student begins working on multistep syntheses, he may appreciate a shorter way of representing reactions than the usual chemist's shorthand, the equation. This abbreviated shorthand is the outline form. The examples below, taken from eqs. (54), (55), (57), and (58), should make clear how the outline form is written.



An outline is *not* an equation. There is no attempt to justify the law of conservation of mass by balancing. An outline, therefore, must not be used in a problem that requests an equation.

SUPPLEMENTARY READINGS

- Dye, J. L., "Model of a Potential Energy Surface," *J. Chem. Educ.* **34**, 215 (1957).
- Ferguson, L. N., *Electron Structures of Organic Molecules*, Prentice-Hall, Englewood Cliffs, N. J., 1952, Chapter 2, "Types of Chemical Bonds"; Chapter 4, "Covalent Bond Distances and Bond Angles"; Chapter 5, "intramolecular Forces"; Chapter 8, "Resonance and Its Applications to Organic Chemistry."
- Gould, E. S., *Mechanism and Structure in Organic Chemistry*, Holt-Dryden, New York, 1959, chapters 5, 6, and 7.
- Hine, J., *Physical Organic Chemistry*, 2nd Ed., McGraw-Hill, New York, 1962, Chapters 1 and 3.
- Ingold, C. K., *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, §6d-7f, pp. 43-92, and §15-§16g, pp. 198-220.
- King, E. L., *How Chemical Reactions Occur*, Benjamin, New York, 1963.
- Noller, C. R., "A Physical Picture of Covalent Bonding and Resonance in Organic Chemistry," *J. Chem. Educ.* **27**, 504 (1950).

QUESTIONS AND PROBLEMS

1. Define and illustrate the following terms.

- | | |
|-----------------------------|--------------------------|
| a. energy of activation | g. reactive intermediate |
| b. contact catalyst | h. transition state |
| c. complex-forming catalyst | i. ΔH^\ddagger |
| d. cross conjugation | j. ΔF^\ddagger |
| e. electrophile | k. steric acceleration |
| f. nucleophile | l. steric hindrance |

2. Show how you would ascertain from the elements of which the following compounds are composed whether the compounds are mainly electrophilic or nucleophilic.

- | | |
|------------------------------|-----------------------------|
| a. COCl_2 | d. CH_3NH_2 |
| b. CH_3SCH_3 | e. PCl_5 |
| c. C_2H_4 | f. NaOH |

3. How does raising the temperature of a reacting mixture increase the rate of the reaction? Why does raising the temperature of the mixture sometimes cause a different reaction to occur than that which occurs at the lower temperature?

4. Starting with acetylene as the only organic raw material, outline the preparation from it and its products of as many organic compounds as you can in fifteen minutes. Indicate necessary reagents and special conditions. No alkanes are to be used as synthetic intermediates. Why? Alkanes may, of course, be products.

5. Differentiate between a transition state and a reactive intermediate on the basis of

- | | |
|--|--------------------------------------|
| a. position on the reaction coordinate | c. influence on the rate of reaction |
| b. duration of existence | d. ease of detection |

6. Is it proper to say that absolutely free rotation exists about a single bond in an alkane? Why?

7. Write equations to show reactions by which the configurations of the 2-butenes can be established, using the butenedioic acids as reference compounds.

8. Referring to the table of bond dissociation energies (Table 11-1), predict the relative ease of halogenation at the various positions of the following compounds by a reaction that requires dissociation of a carbon-hydrogen bond by a halogen atom.

a. isopentane b. ethylbenzene

9. Considering the bond energies of the HCl and HBr molecules (Table 11-2), predict the relative selectivities of a Cl atom and a Br atom attack as in Problem 9.

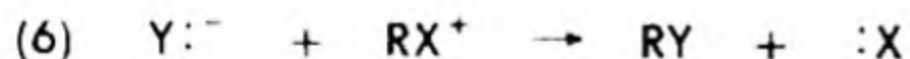
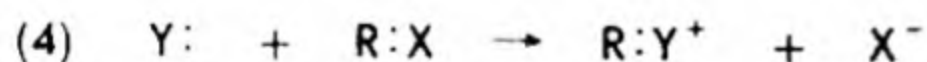
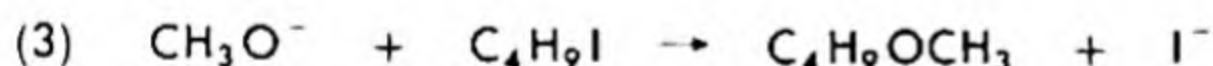
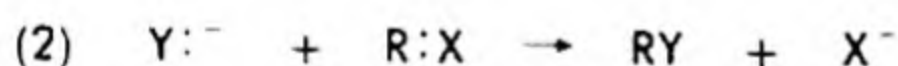
12

Nucleophilic Displacements on Saturated Carbon Atoms

12-1 REPLACEMENTS OF HALIDES, SULFATES, AND SULFONATES

A. General Nature of These Reactions

This chapter deals with one of the most common general types of organic reactions, in which one atom or group bonded to a saturated carbon atom is displaced along with its bonding electron pair by another group which donates an electron pair. Since the electron-pair-donor reagent is termed a nucleophile (§11-5), the reaction is termed a *nucleophilic displacement reaction*. The general equation for this reaction is given in eq. (1), where n and m represent the charges of $Y:$ and $R:X$, respectively. Some examples of different charge type are given in eqs. (2) through (7); others are possible.



(1) *Nucleophilic Agents.* Any substance which has unshared electron pairs (or potential unshared electron pairs) is capable of acting as a nucleophile. This is the same definition used for Brønsted or for Lewis bases. Now, however, we are concerned with reactions of nucleophiles other than acid-base reactions. Among the important nucleophilic agents are the ions: OH^- , OR^- , OAr^- , SH^- , SR^- , SAr^- , S^{2-} , RCO_2^- ,

$C\equiv N^-$, $RC\equiv C^-$, $HC\equiv C^-$, $C\equiv C^{2-}$, $O=C=N^-$, $S=C=N^-$, $O=N-O^-$, R_3C^- , R_2N^- , Cl^- , Br^- , and I^- . These are often used as the sodium or potassium salts, but some are also used as silver or other salts.

Uncharged molecules may also act as nucleophiles; among the common ones are ammonia and amines, NH_3 , RNH_2 , R_2NH , R_3N ; thioethers, R_2S ; water, H_2O ; alcohols, ROH ; and acids, RCO_2H .

(2) *Nature of the Displaced Group.* Just as there are many possibilities for the nucleophile $Y:$, there are a great many groups, called *leaving groups*, that are displaceable and can be the $:X$ in the RX species. Among the uncharged RX molecules most generally used are RCI , RBr , RI ,

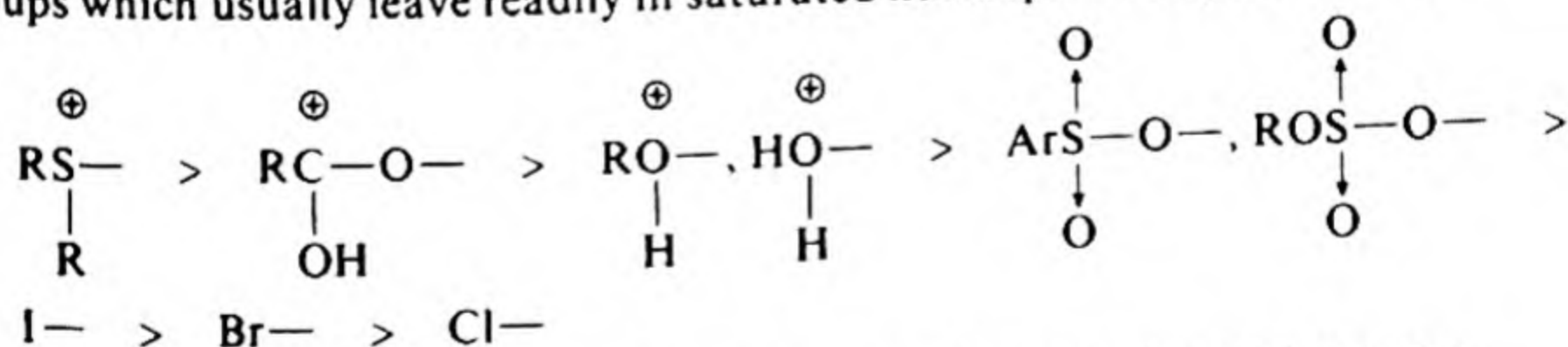
$ROSO_2OR$, and $ROSO_2Ar$, while charged RX^+ species include ROH_2^+ , ROR^+ , $RCOOR^+$, RSR_2^+ and RNR_3^+ . This reaction type thus includes

certain reactions of alkyl halides, sulfates, sulfonates, alcohols, ethers, esters, sulfonium compounds, and ammonium compounds, among others. A list of leaving groups in approximate order of ease of removal is given in Table 12-1.

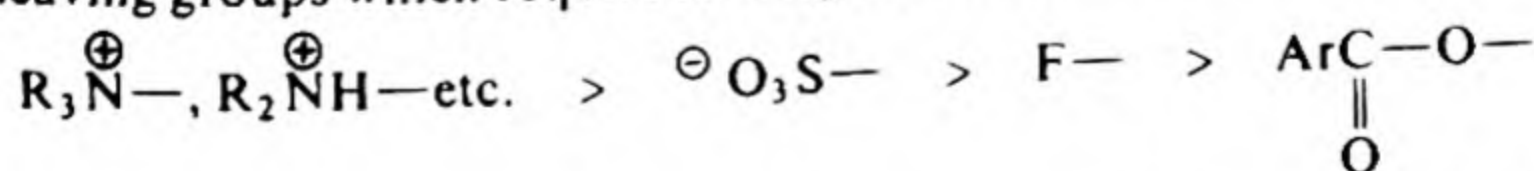
It may be noted that several leaving groups are more readily displaced than halide atoms; those capable of reacting in basic media include sulfonates and sulfates. The ease with which halide ions leave is in the order $I^- > Br^- > Cl^-$. Fluorides are generally quite inert. The hydroxy group $-OH$ is converted to $-OH_2^+$, an excellent leaving group, do "hydroxy" displacements occur.

TABLE 12-1. Leaving Groups

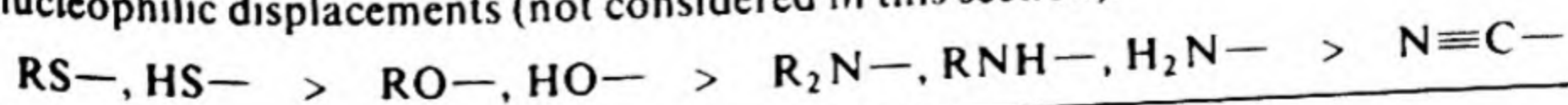
Groups which usually leave readily in saturated nucleophilic displacements:



Poorer leaving groups which require forcing conditions in saturated systems:



Very poor leaving groups, involved only in certain special types of *unsaturated* nucleophilic displacements (not considered in this section):



B. Mechanisms of Nucleophilic Displacement Reactions

There appear to be two general pathways for nucleophilic displacements. Experimental evidence is available to suggest that each mechanism operates under certain sets of conditions, that occasionally both mechanisms may operate at once, or that in some borderline cases the mechanism may be also borderline between the two extremes.

(1) *Direct Displacement Process.* One of these mechanisms is called the direct-displacement process, symbolized S_N2 , and is a one-stage process in which $Y:$ attacks the carbon atom in $R:X$ as $:X$ leaves (eq. (8) and Fig. 12-1). The symbolism means substitution, S; nucleophilic, N; bimolecu-

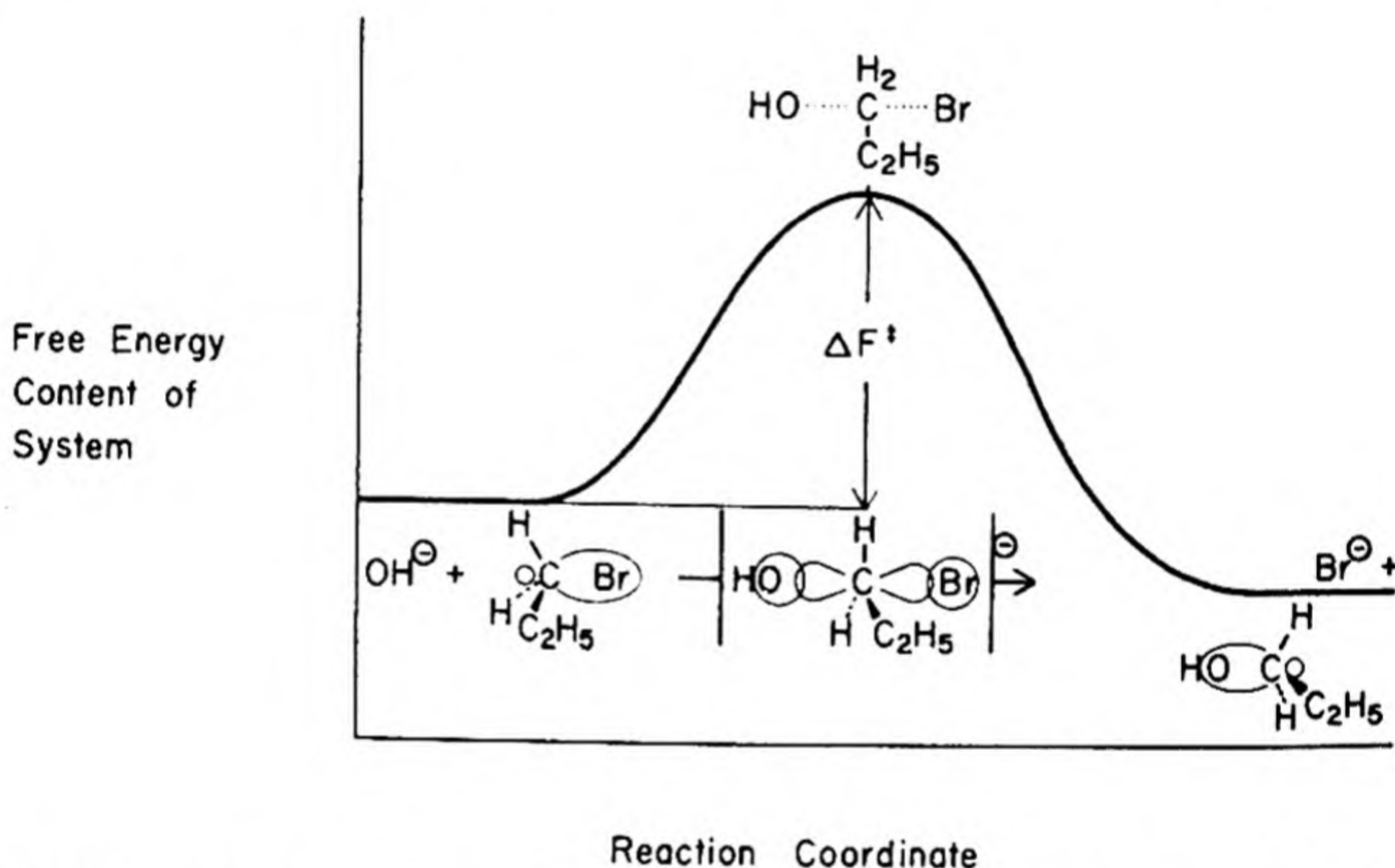
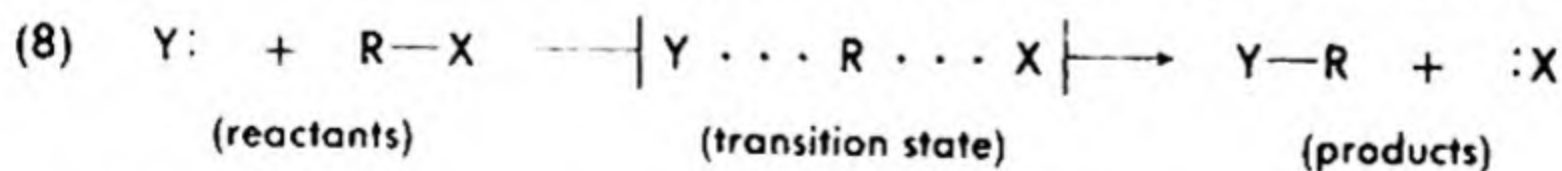


Fig. 12-1. Free Energy Diagram for a Direct Displacement Reaction, n -Propyl Bromide ($R-X$) and Hydroxide (nucleophile $Y:$).

lar, 2 (since two molecules change covalences in the rate-determining step). This mechanism is favored by relatively open access to the back of



the carbon atom undergoing displacement. This carbon atom undergoes inversion of configuration, called *Walden inversion* (§31-9C). The reagent $Y:$ attacks the back face of the tetrahedron opposite to the corner at which the X group is attached, whereupon the other groups on the carbon atom move into and then cross the plane containing the carbon atom and perpendicular to the $Y \cdots C \cdots X$ axis (Fig. 12-2) like an umbrella

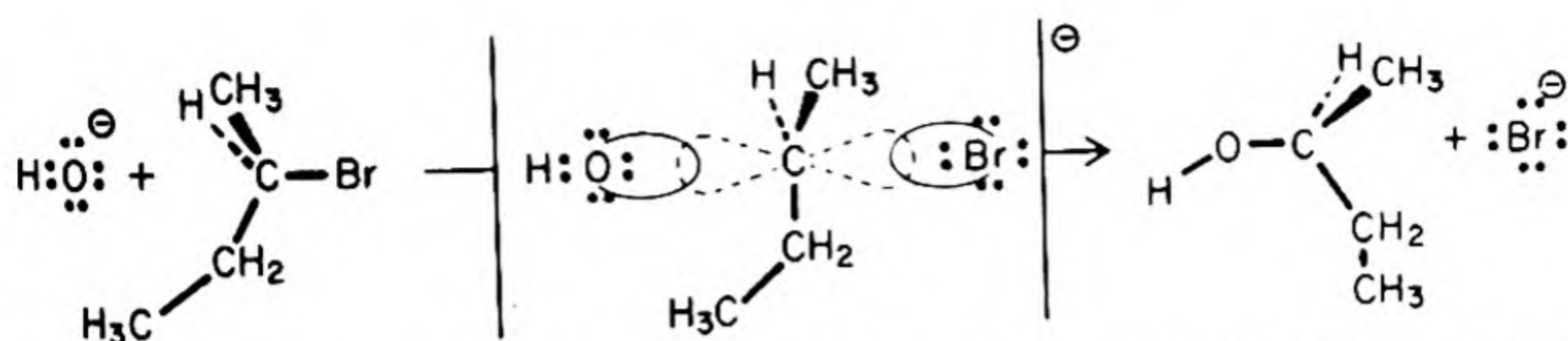


Fig. 12-2. Inversion of Configuration in Direct Displacement by Hydroxide Ion of Bromide in 2°-Butyl Bromide. One representation of MO of transition state, in which the p orbital of functional carbon is involved with electrons of both bromide and hydroxide. Note backside attack of hydroxide and inversion of hydrogen atoms and ethyl group on propyl chain.

turning inside out in a high wind. Walden inversion can be observed experimentally in cases where there are four different groups on the functional carbon atom.

As there are no intermediates in this reaction, the transition state (§11-3C) contains Y and RX , and the reaction is first order in RX and first order in Y , total order two. The rate expression is given in eq. (9). One should note that the key to reactivity in this type of reaction is a combination of the ability of $Y:$ to attack RX and the ability of the $R-X$ bond to be cleaved heterolytically.

$$(9) \quad \text{Rate} = k[RX][Y]$$

(2) *Carbonium Ion Process.* The second of the two general processes for nucleophilic displacement is a multistage process, symbolized S_N1 (nucleophilic substitution, unimolecular) in which a *carbonium ion* is an intermediate.

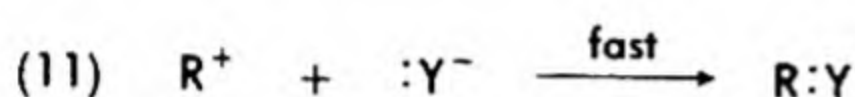
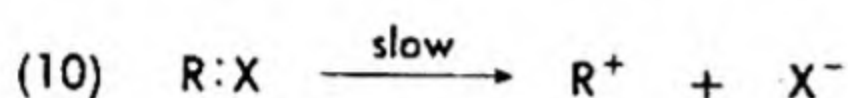
A carbonium ion, R_3C^+ , contains a carbon atom which has only six electrons in its valence shell and which has a positive charge. The three $C-R$ σ bonds utilize sp^2 atomic orbitals on carbon (§4-1) and the remaining orbital, which is empty, is a p orbital. The result of this hybridization is that a carbonium ion is planar (Fig. 12-3).

In its simplest form, the reaction may be said to involve two parts, a



Fig. 12-3. MO Cloud and MO Formula of a Carbonium Ion. The dotted orbital is empty.

(generally) rate-determining ionization (eq. 10) followed by rapid coordination with nucleophile (eq. 11). When the first step is the slower, as its transition state contains only the RX reactant, the reaction is first order in RX and zero order in Y^- —that is, the reaction rate is independent of the concentration of Y^- (eq. 12). This is a principal test for distinguishing the carbonium ion process from the direct displacement process. In addition, there is the important consequence that the nature and concentration of the nucleophile have no influence on the rate, so long as the reaction occurs by the S_N1 process.



The solvent plays a very important role in such reactions. In the initial part of the reaction, ionization is facilitated through the solvation of the cation by at least one solvent molecule and of the anion by at least one other solvent molecule. The solvated *ion pair* (see next paragraph) which results is shown descriptively in Fig. 12-4C, with water shown as solvent. One molecule of water interacts at the negative end of its dipole with the carbonium ion and the other water molecule at its hydrogen atom with the anion. These stabilizing factors lower the energy of the ion pair and of the transition state leading to the ion pair. The importance of solvation is indicated by the data in Table 12-2. The solvent may react with the carbonium ion before the ion pair dissociates, or the ion pair may alternatively dissociate to symmetrically solvated ions (Figs. 12-4 and 12-5).

Ionization of a covalent molecule in solution occurs by a process rather different from the dissolving of an already ionic salt lattice. If the molecule forms stable ions in solution (e.g., HCl in water, $(C_6H_5)_3CCl$ in sulfur dioxide), several stages are involved. Each molecule is at first surrounded

TABLE 12-2. Ionization and Solvation Energies for Alkyl Bromides in Water

R	ΔH for $R-Br \rightarrow$ Gaseous Ions, $R^+ + Br^-$, kcal./mole ^a	ΔH for Gaseous $R^+ + Br^- \rightarrow$ Solvated Ions, kcal./mole	Net ΔH for $R-Br \rightarrow$ Solvated Ions, $R^+ + Br^-$, kcal./mole ^b
Methyl	221	—	—
Ethyl	180	-150	30
Isopropyl	158	-130	28
3°-Butyl	138	-115	23

^a Data from mass spectra.

^b Data from S_N1 hydrolysis rates (not available for methyl bromide)

by solvent molecules (Fig. 12-4A) which form a wall called the solvent cage. With help from the solvent, ionization occurs to form an *intimate ion pair* or *tight ion pair*, in which the ions are still connected electrostatically and are in the same solvent cage (Fig. 12-4B). Next, solvent molecules move in to surround the ions to form a larger aggregate, called

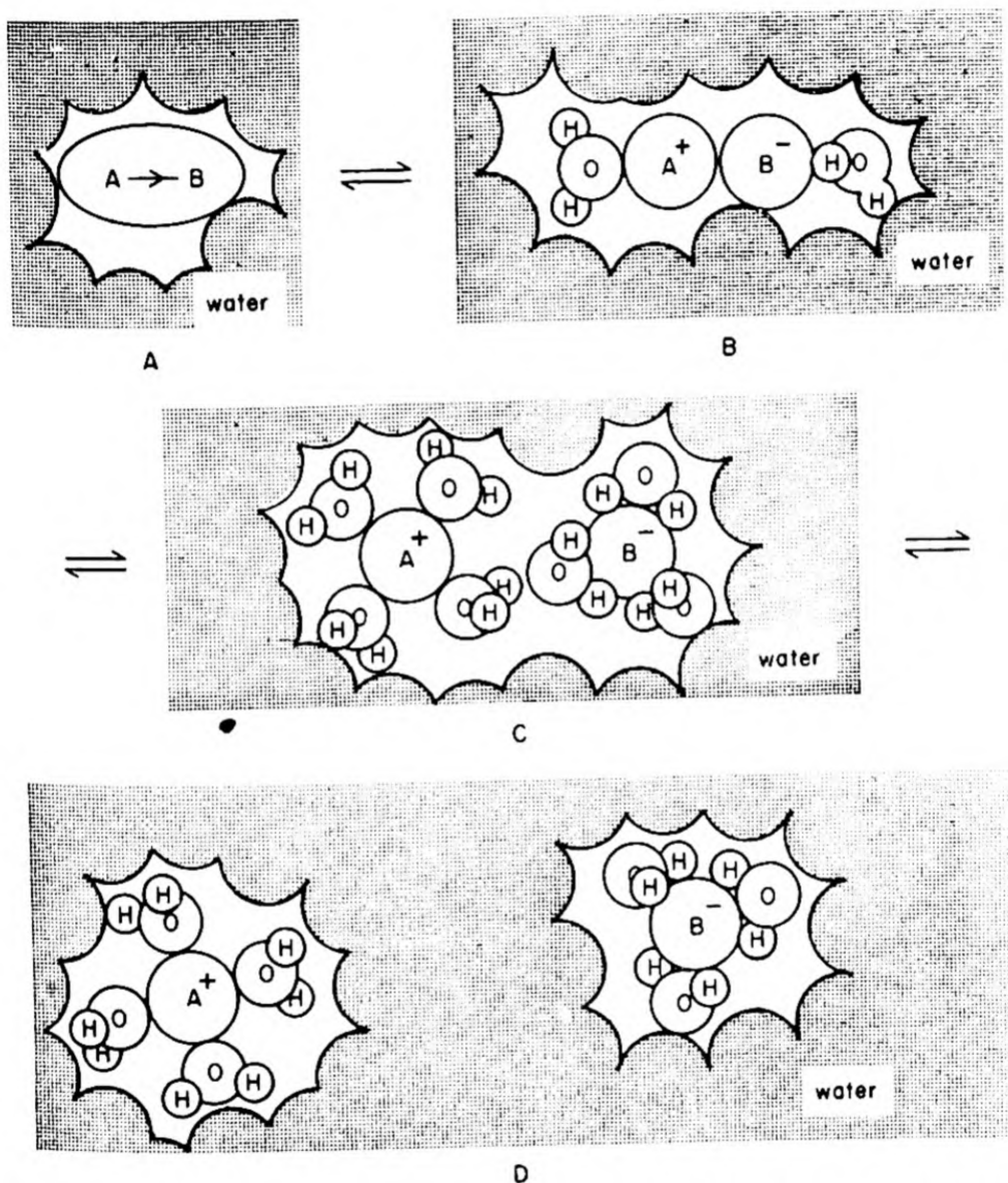


Fig. 12-4. Steps in Ionization of a Covalent Molecule. (A) Polar molecule ($A-B$) surrounded by solvent molecules (cross-hatch), (B) Intimate, tight, or internal ion pair together in same solvent cage, (C) Solvated or external ion pair, still in same solvent cage, (D) Dissociated or separate ions, solvated and separated by solvent (cross-hatch).

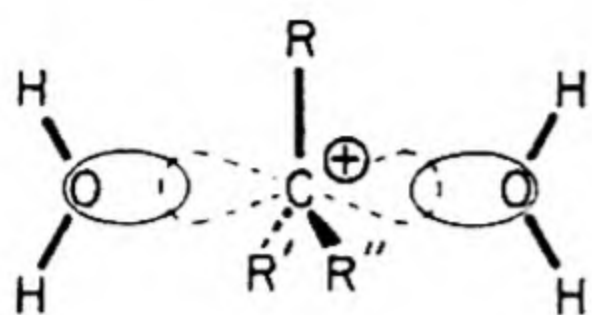


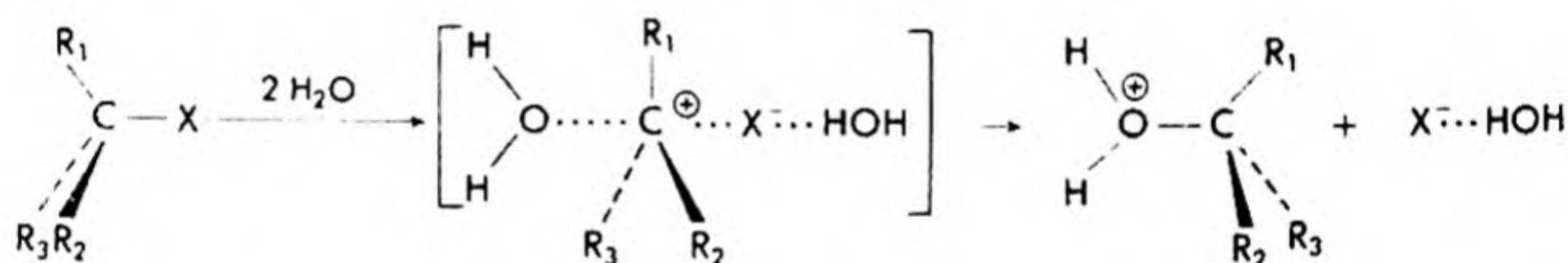
Fig. 12-5. A Symmetrically Solvated Carbonium Ion.

a *solvent-separated ion pair*, still inside a (now larger) solvent cage (Fig. 12-4C). Finally, the solvated ions move into separate portions of the solution to form *dissociated ions* (Fig. 12-4D).

Many organic ionization processes go only part way in this scheme of carbonium ions. Thus, a reaction utilizing the S_N1 mechanism may go only to the tight ion pair, after which, if not at once attacked by a nucleophile, the ion pair collapses back to a covalent molecule. In other cases, however, the carbonium ion intermediate which ultimately reacts with the nucleophile is the solvated ion pair or completely dissociated ion.

Any reaction which occurs at the tight-ion-pair stage gives inversion of configuration (eq. 13), as the solvent which forms the covalent bond to the

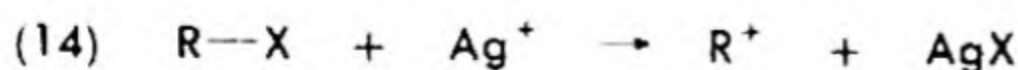
(13)



cationic carbon atom is present at the back of the carbon atom opposite to the original $C-X$ bond. If the covalent bond with solvent or with other nucleophiles forms after the planar cation is symmetrically solvated (Fig. 12-4D), reaction is equally likely from either the back (inversion) or front (retention of configuration) and the resulting product has mixed configurations when four different groups are present (§31-3). Some carbonium-ion reactions give much inversion, but generally such reactions are attended with considerable racemization (mixing of configurations).

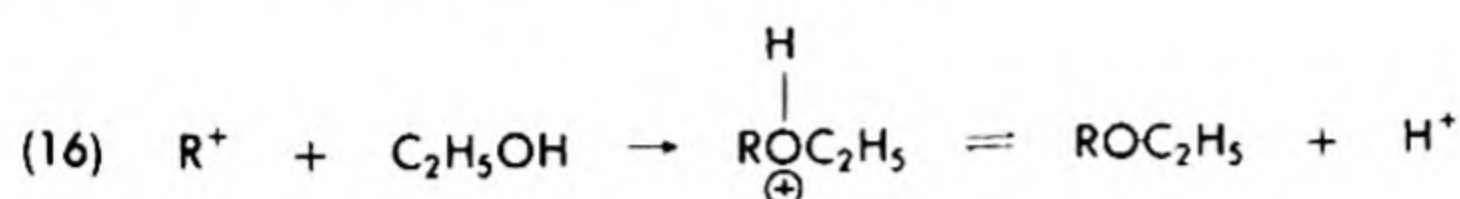
Carbonium ion reactions typically are often accompanied by molecular rearrangements, some examples of which are given in §12-2 below, and also by olefin formation.

(3) *The Role of Metal Ions in Nucleophilic Displacements.* The silver ion, unlike the sodium ion, is an effective electrophile toward halogen (although not toward sulfates or sulfonates). This means that silver ion is an effective catalyst for carbonium ion processes (eq. 14) of alkyl halides, so



(X = halogen only)

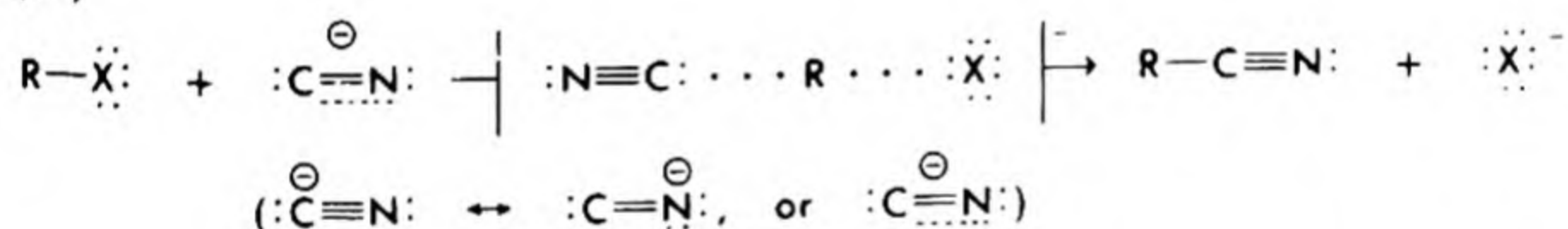
that the reaction of, for example, silver nitrate with many halides is much faster than that of sodium nitrate. In ethanol, the products are the alkyl nitrate and the alkyl ethyl ether (eqs. 15 and 16).



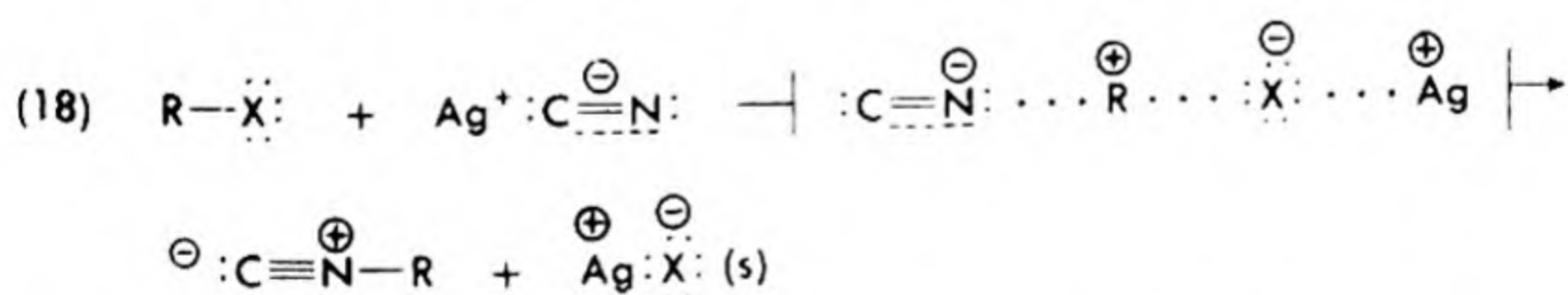
This difference in behavior of the silver ion can result in important differences in products when the silver salts are used instead of alkali metal salts. For example, treatment of a halide with sodium cyanide gives mainly a nitrile. Use of silver cyanide, however, may result largely in the formation of an isonitrile (carbylamine). Sodium cyanide operates only by the nucleophilic push of the cyanide ion on the functional carbon to displace the halide atom, thus favors the direct displacement mechanism. The attacked carbon atom in the halide is thus only mildly electrophilic and most successfully forms a bond at the carbon atom of the cyanide ion

that atom with the stronger tendency to be covalent (greater nucleophilicity) (eq. 17). In the silver salt, however, the electrophilic silver ion exerts a pull on the halogen atom. The carbonium ion character of the

(17)

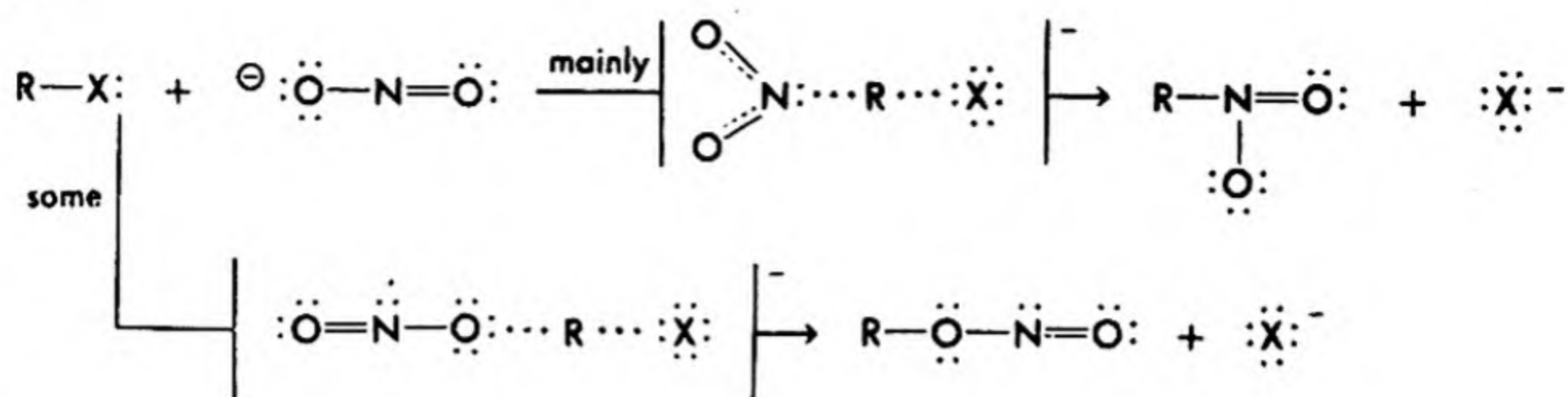


process is thus increased to make more probable bond formation at the more electronegative nitrogen atom (eq. 18) since the positive carbonium ion is strongly attracted by *negative charge*, not nucleophilicity.

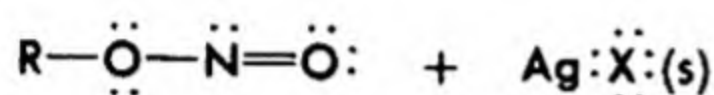
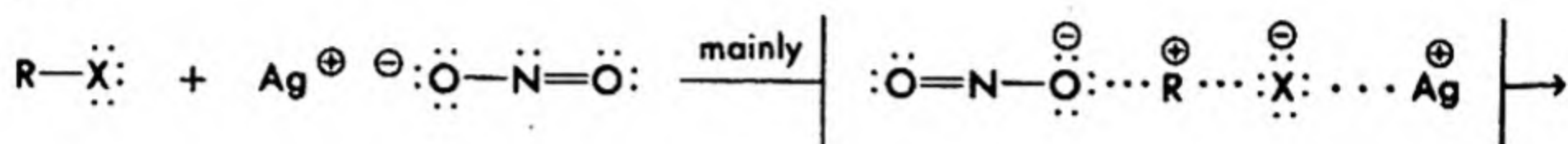


A similar effect is responsible for the higher yields of nitrite esters obtained from silver nitrite than from alkali nitrites. The negative charge on the oxygen atom of the nitrite ion makes this the position more attractive to a complex of considerable carbonium ion character, whereas the nitrogen atom, more prone to covalence, forms the more stable bond when the silver ion is not present to exert a pull on the halogen atom.

(19)



(20)



(4) *Influence of Hydrocarbon Groups on Mechanism of Replacement.* Donation of electrons by alkyl groups attached to the functional carbon atom stabilizes a positive charge on that carbon atom, thus facilitates ionization in the order methyl < ethyl < isopropyl < 3°-butyl. In the same order, the increasing number of alkyl groups on the functional carbon atom *decreases* that atom's availability from the rear, hence decreases the ease of formation of a transition state for direct displacement. (See Fig. 12-6.) Consequently, a methyl halide, with little tendency to ionize, and with only small hydrogen atoms on the carbon atom, reacts well by the direct displacement mechanism, but very slowly by the carbonium ion mechanism. Conversely, 3°-butyl halides, with relatively strong tendency

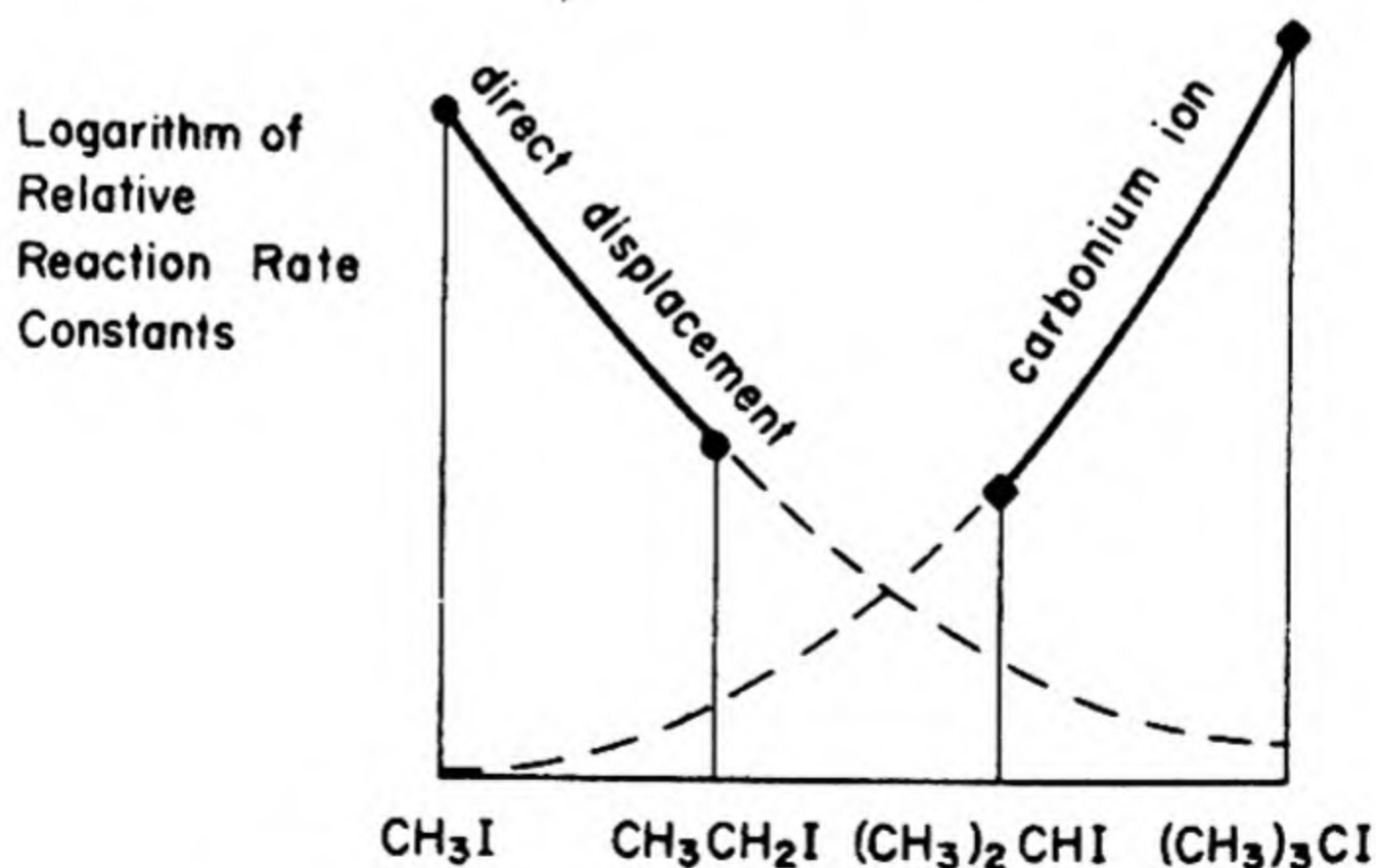


Fig. 12-6. Relative Rates of Hydrolysis of Alkyl Halides by Different Mechanisms.

to ionize, but with the access to the functional carbon atom largely blocked, react rapidly by the carbonium ion mechanism, but very slowly via a direct displacement. Simple primary, secondary, and tertiary halides show increasing tendency to react by the carbonium ion mechanism and decreasing tendency to react by direct displacement.

Since steric requirements of the transition state in direct displacement are higher, while those of the transition state in the carbonium ion process are lower than those of the original halide, bulky alkyl groups favor the latter mechanism (see §12-1B(1) and §12-1B(2) above).

There appear to be two methods of electron release from saturated alkyl groups to stabilize cationic centers. The first, and generally accepted one, is that of *inductive release* (see §10-2A) in which the positive charge on the carbonium ion induces a charge transfer in the R—C bonds, which are more polarizable (because of greater size and number of electrons) than H—C and thus can better stabilize a positive charge (Fig. 12-7). Another hypothesis is that the *sigma* electrons of a C—H bond (and to a lesser extent a C—R bond) can be delocalized into the empty *p* orbital of the carbonium ion (Fig. 12-8). This mode of electron release is called *hyperconjugation* or *no-bond resonance* and like all electron delocalization is stabilizing. Its existence is still unproved, but there is some evidence which may require such an explanation.

Those groups which are electron withdrawing lower the stability of carbonium ions and retard the carbonium ion process. The same groups

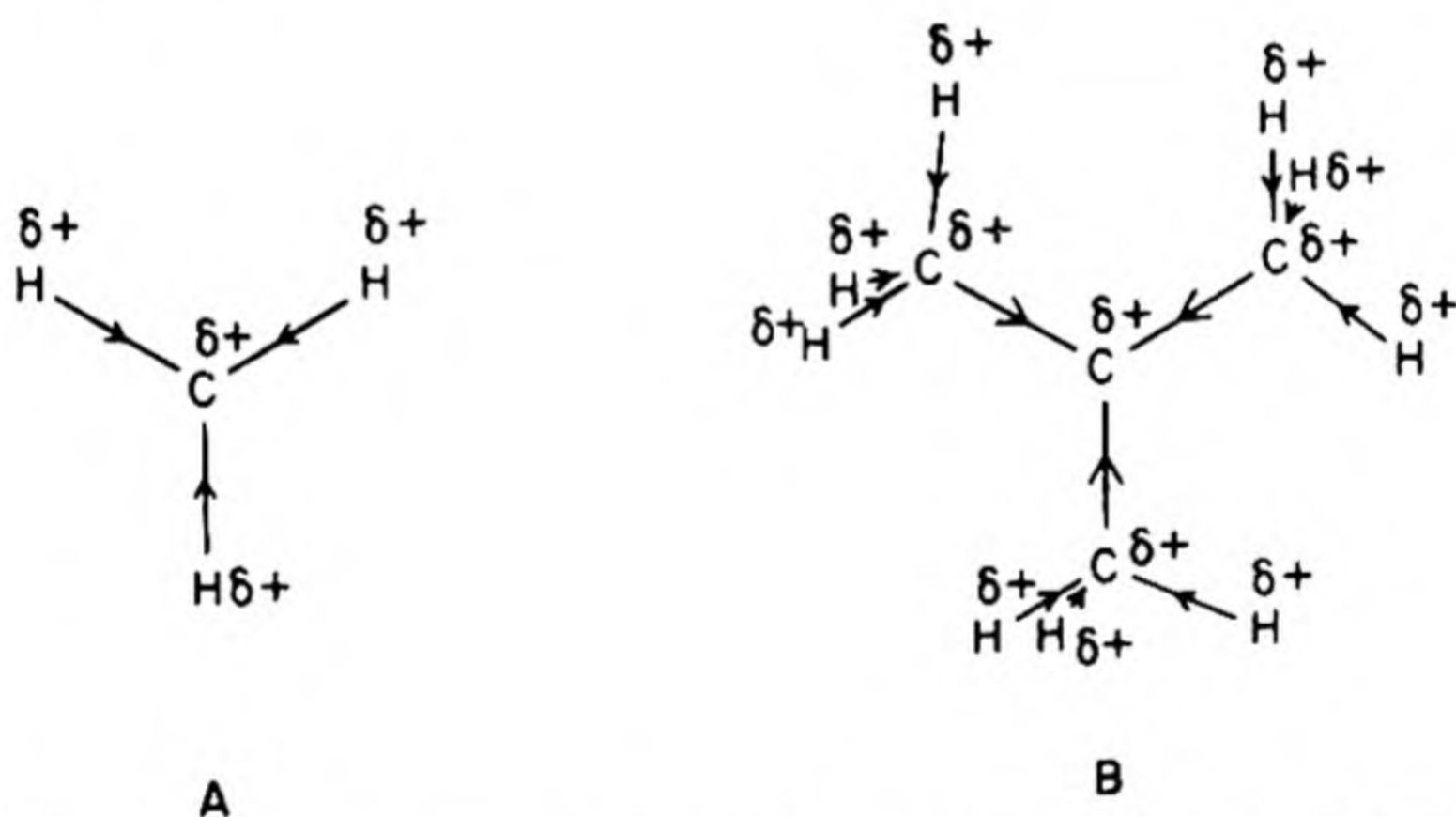


Fig. 12-7. Stabilization of Positive Charge in a Carbonium Ion by the Inductive Effect, (A) Carbonium ion, capable of delocalization of charge into only three atoms—very unstable ion, (B) Trimethylcarbonium ion, in which induction of charge from adjacent carbon atoms is aided by second stage induction from hydrogen atoms—relatively more stable. Charge delocalized into twelve atoms. Center carbon atom in each case is formally positive.

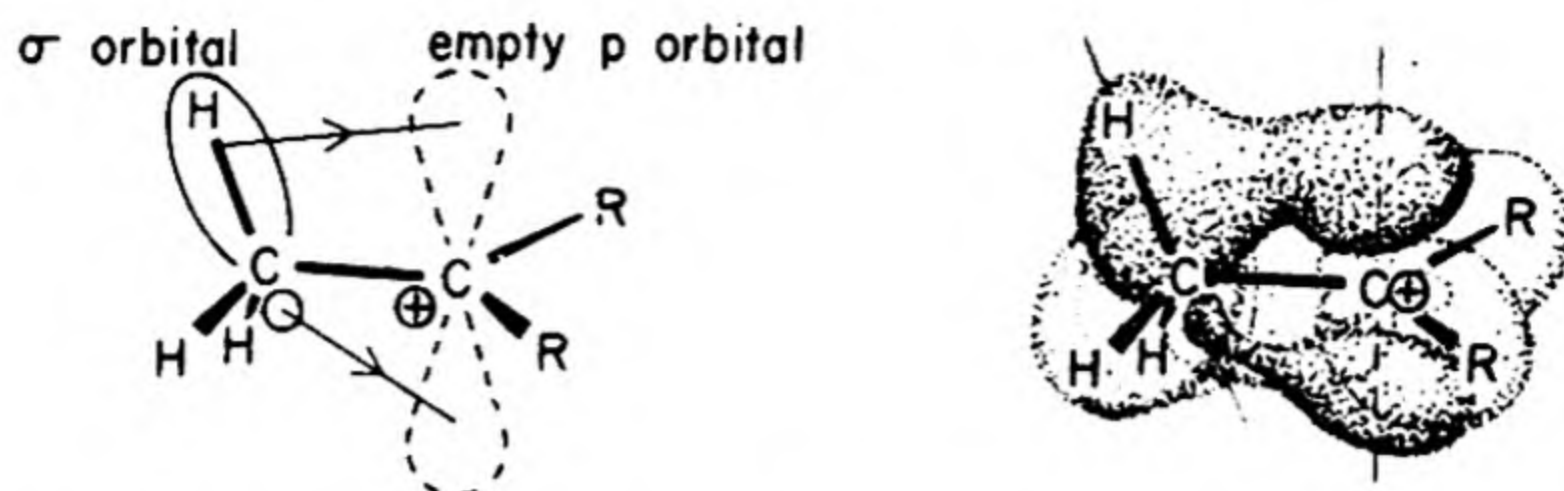
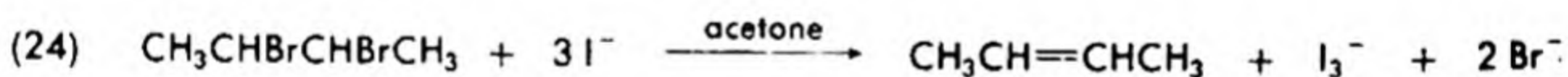
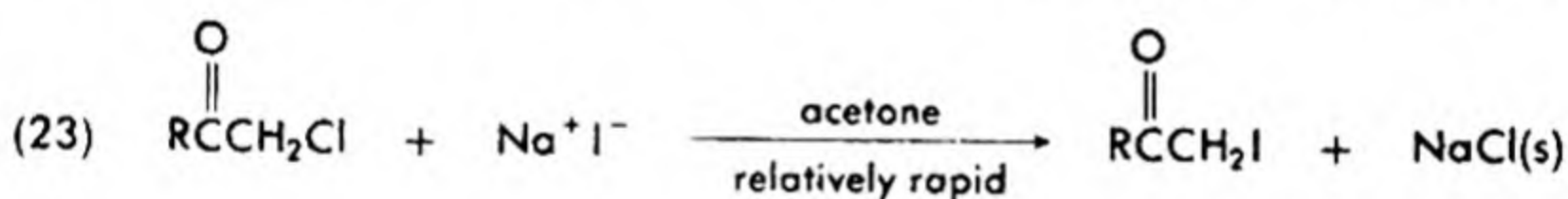
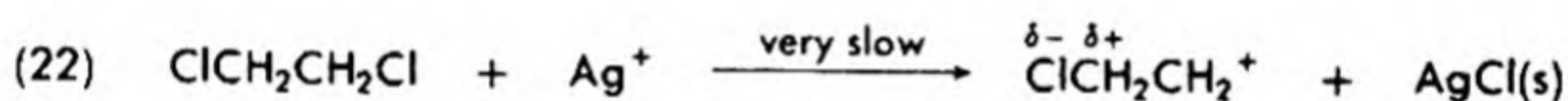
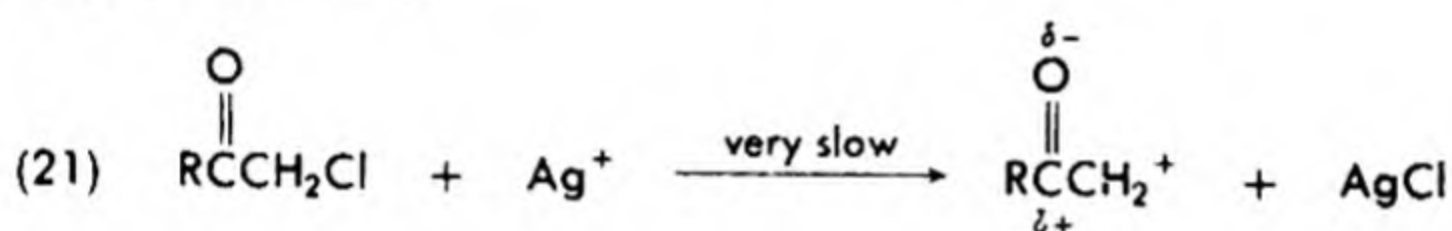


Fig. 12-8. MO Formula and MO Cloud Representing Hyperconjugation. While only one C—H bond participates, the probability of a favorable conformation is greater the larger the number of α -hydrogen atoms.

sometimes facilitate nucleophilic attack, thus often increase the rate of the direct displacement process. Thus, α -chloroketones and vicinal dichlorides do not react rapidly with silver ion (eqs. 21 and 22), a carbonium ion process, but react with some facility with potassium iodide in acetone (eqs. 23 and 24).

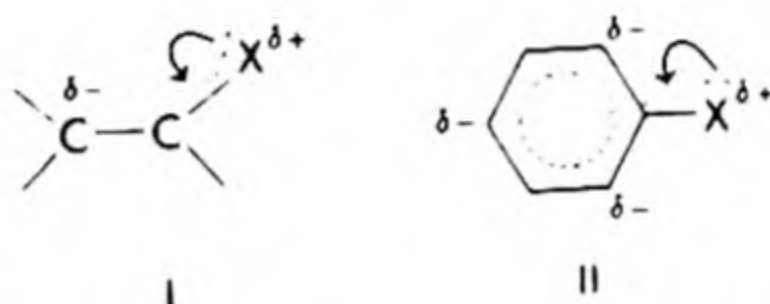


It may be noted that *vic*-dibromides and dichlorides generally give olefins and free iodine. Ethanolic silver nitrate is often used as a diagnostic reagent to measure reactivity of alkyl halides by the carbonium ion process. Sodium iodide in acetone is used to measure reactivity in direct displacement processes. As precipitates are formed (sodium chloride and bromide are insoluble in acetone), one can measure the relative rates of reaction by the length of time it takes them to appear.

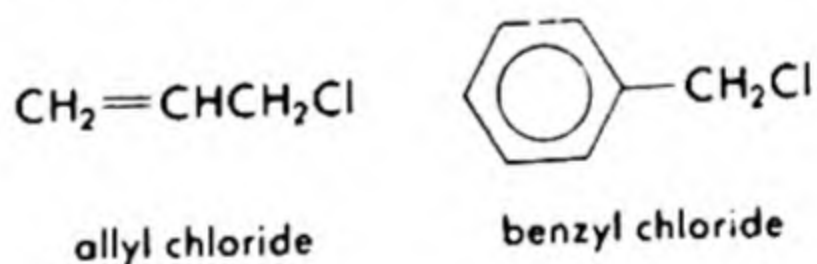
The reactions in eqs. (21) and (22) would be slow as the transition states leading to the carbonium ion intermediates require a positive charge to be developed on a carbon atom next to another carbon atom which already has a large fraction of a positive charge (positive end of a $\text{C}=\text{O}$ or a $\text{C}-\text{Cl}$ dipole). Thus, strong electrostatic destabilization is involved. The opposite effect is noted in the transition state for the direct displacement process, where in effect an electron pair is added to the system around the

functional carbon atom. However, too much positive character around the functional carbon atom may also hinder the leaving group from moving away from carbon to form the transition state. Which effect prevails depends to some extent on the relative stabilities of the attacking nucleophile and the leaving group.

Unsaturation affects halides, sulfonates, and sulfates in various ways, depending on the position of the multiple bond relative to the leaving group. If a halogen atom is attached at the double bond (vinyl halides) or directly to an aromatic ring (chloroarenes), it fails to react readily by either the S_N1 or the S_N2 mechanism. When the halide atom or oxygen atom of a leaving group is attached directly to an unsaturated carbon atom, the unshared electron pairs on halogen or oxygen conjugate with the unsaturated system (I and II). Thus, resonance effects strengthen the carbon-halogen bond. Those reactions which can occur are discussed in a later chapter (§21-8).



On the other hand, when the unsaturation or the aromatic ring is removed by one carbon atom from the leaving group, as for example in allyl and benzyl systems, the compound is very reactive, in particular by the



carbonium ion process. Here again the facts are rationalized by resonance stabilization of the carbonium ion and of the transition state leading to it (eq. (25) and Fig. 12-9). The allyl cation has two identical canonical

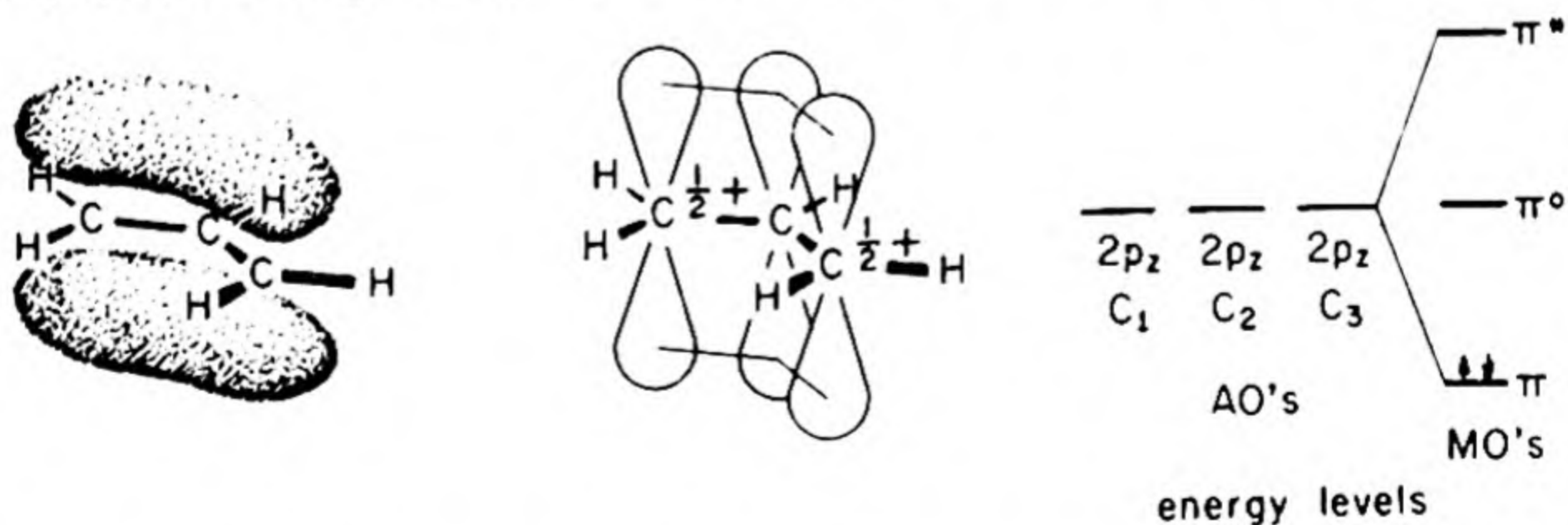


Fig. 12-9. MO Cloud and MO Formula Representing the π Orbital of the Allyl Cation. A two-electron system, hence only one orbital is occupied.

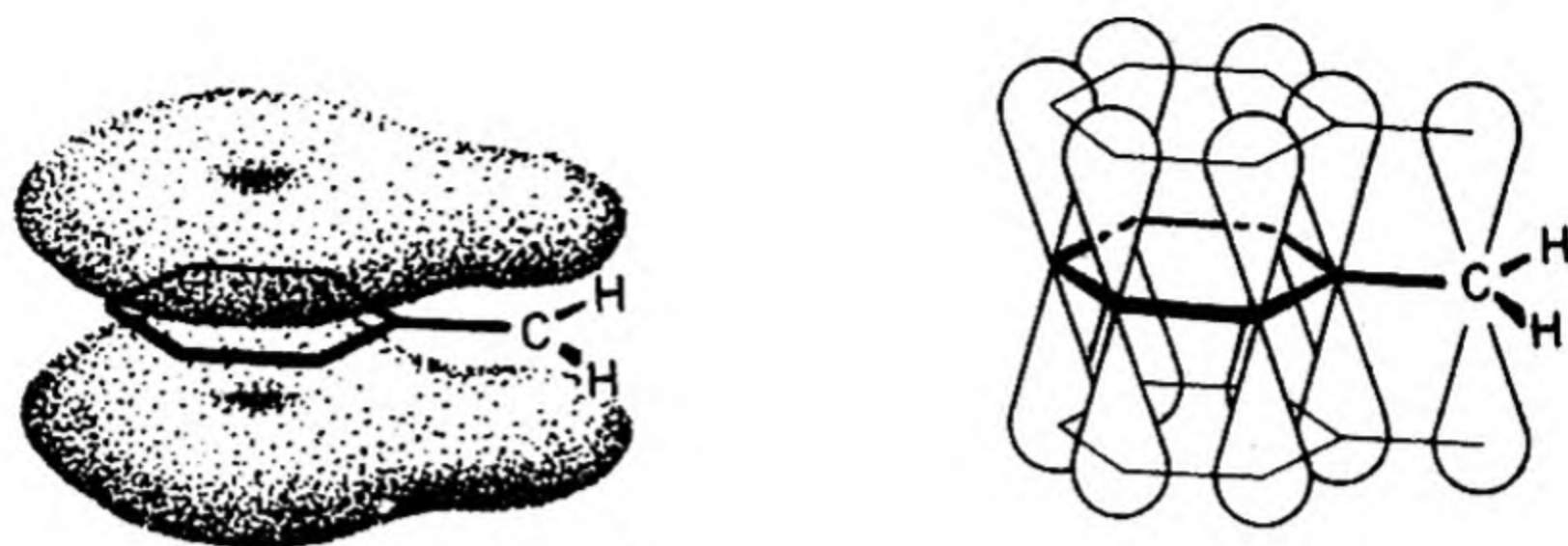
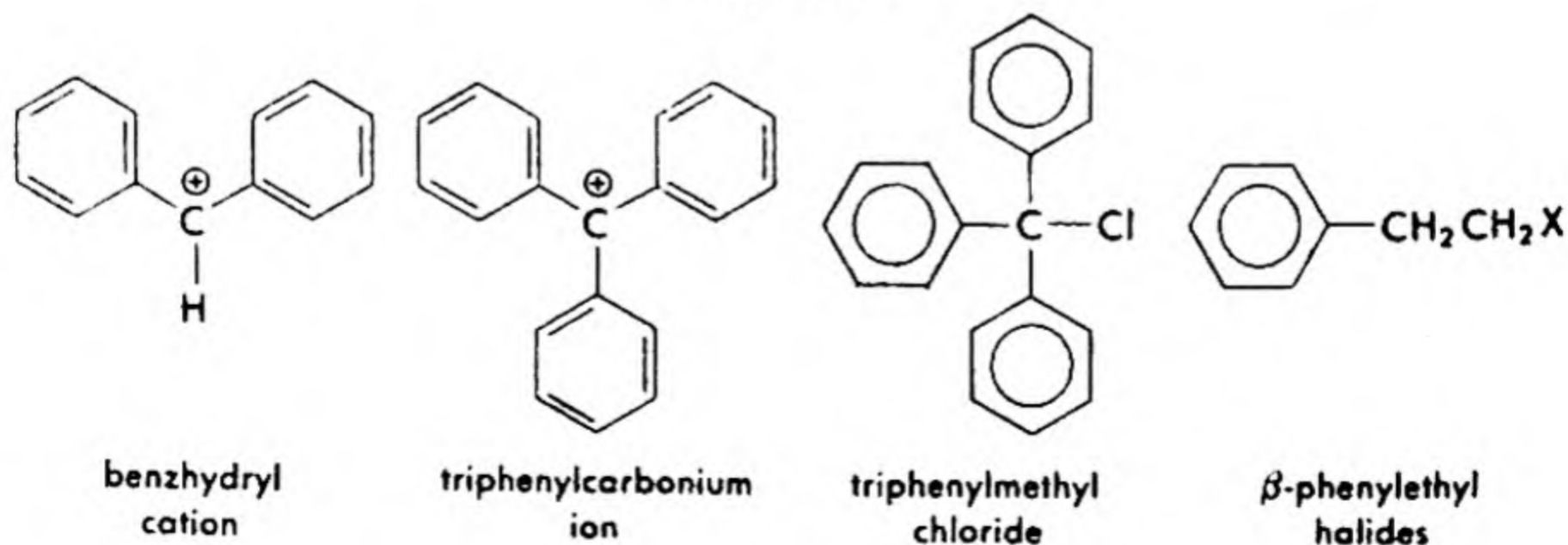
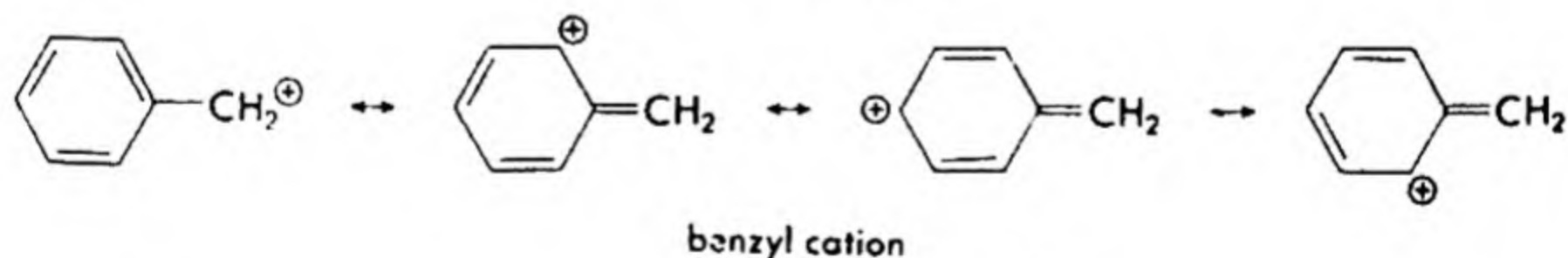
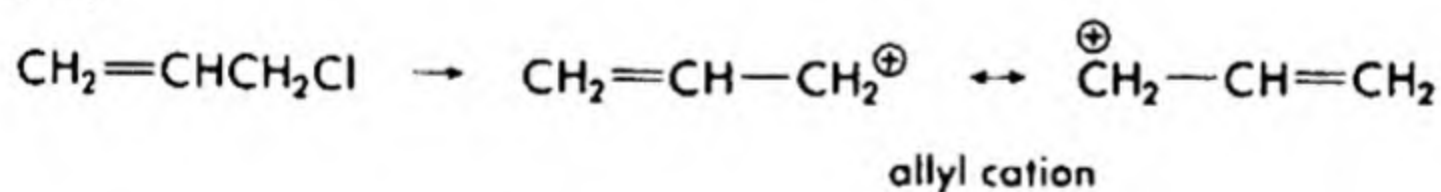


Fig. 12-10. MO Cloud and MO Formula for the Lowest Energy π Orbital in the Benzyl Cation (Phenylcarbonium Ion). Ring hydrogen atoms are omitted. A six-electron system; hence, two more molecular orbitals are required for the π electrons, as in benzene (Fig. 5-18).

forms and is highly resonance stabilized. A similar situation obtains with benzyl cation (see below and Fig. 12-10) where electron delocalization distributes the positive charge over the *ortho* and *para* carbon atoms, hence also gives stabilization. The stabilizing effect of phenyl substitution on the carbonium ion increases with benzhydryl ion (diphenylcarbonium ion) to triphenylcarbonium ion (Fig. 12-11) (where three benzene rings are available for electron delocalization) in ways equivalent to that discussed for the benzyl cation. Resonance stabilization is so effective that triphenylmethyl chloride ionizes to the cation and chloride ion in liquid sulfur dioxide or cresol solutions in amounts sufficient to conduct electricity.

(25)



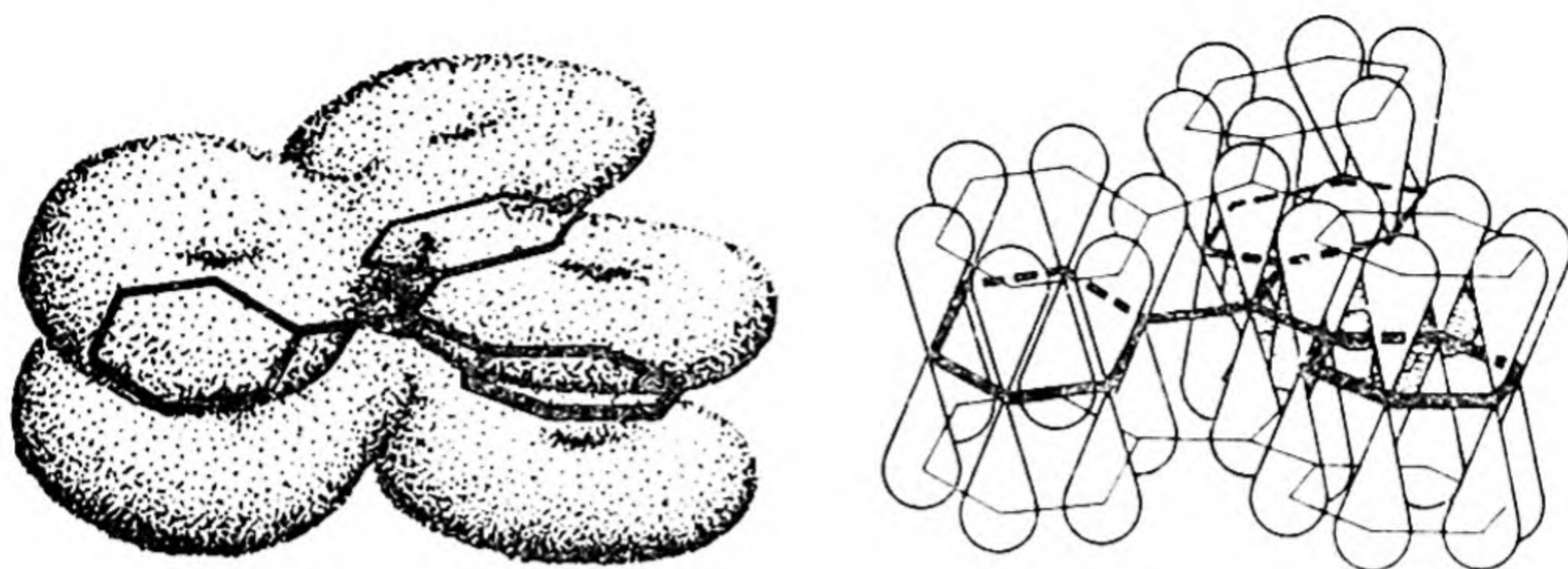
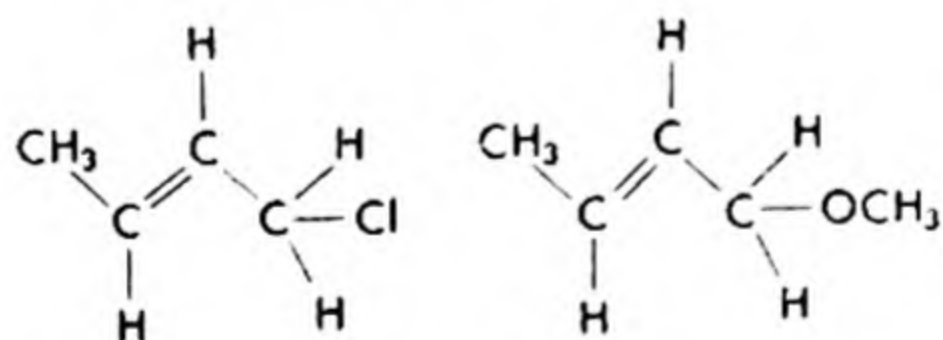


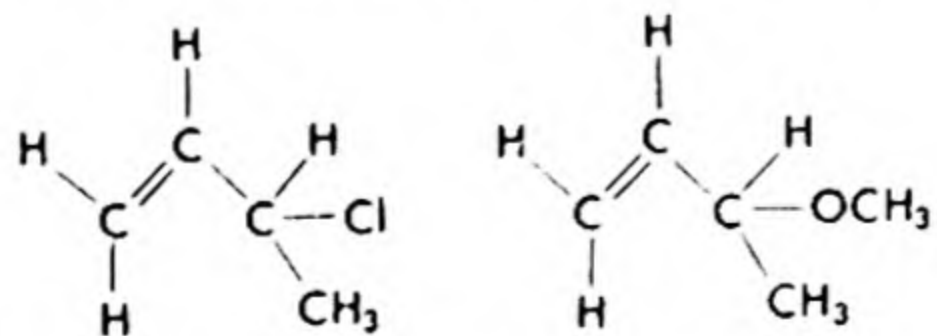
Fig. 12-11. MO Cloud and MO Formula for the Lowest Energy π Orbital for Triphenylcarbonium Ion. Twisting of rings slightly out of the plane of the molecule avoids interference between *ortho* hydrogen atoms. Twisting is not enough to cause loss of much resonance energy. (The MO system for the triphenylmethyl free radical is similar, but involves one more electron.)

These effects of unsaturation are possible only with those carbonium ions on which the allyl or aryl substituent is directly conjugated to the carbonium carbon atom; therefore, such effects are not found when the unsaturated group is insulated from the cationic center by one or more additional atoms. β -Phenylethyl halides, for example, have no exceptional reactivity in nucleophilic displacements.

(5) *Allylic Rearrangements*. It may be expected that a direct displacement on a substituted allylic compound such as *trans*-crotyl (trans- γ -methylallyl) chloride by a nucleophile, for example, methoxide ion, should lead to a normal displacement product, for example, methyl crotyl ether. Similarly, α -methylallyl chloride is expected to give methyl α -methylallyl ether. This is usually the case when the functional carbon atom is relatively unhindered, as it is in these examples.

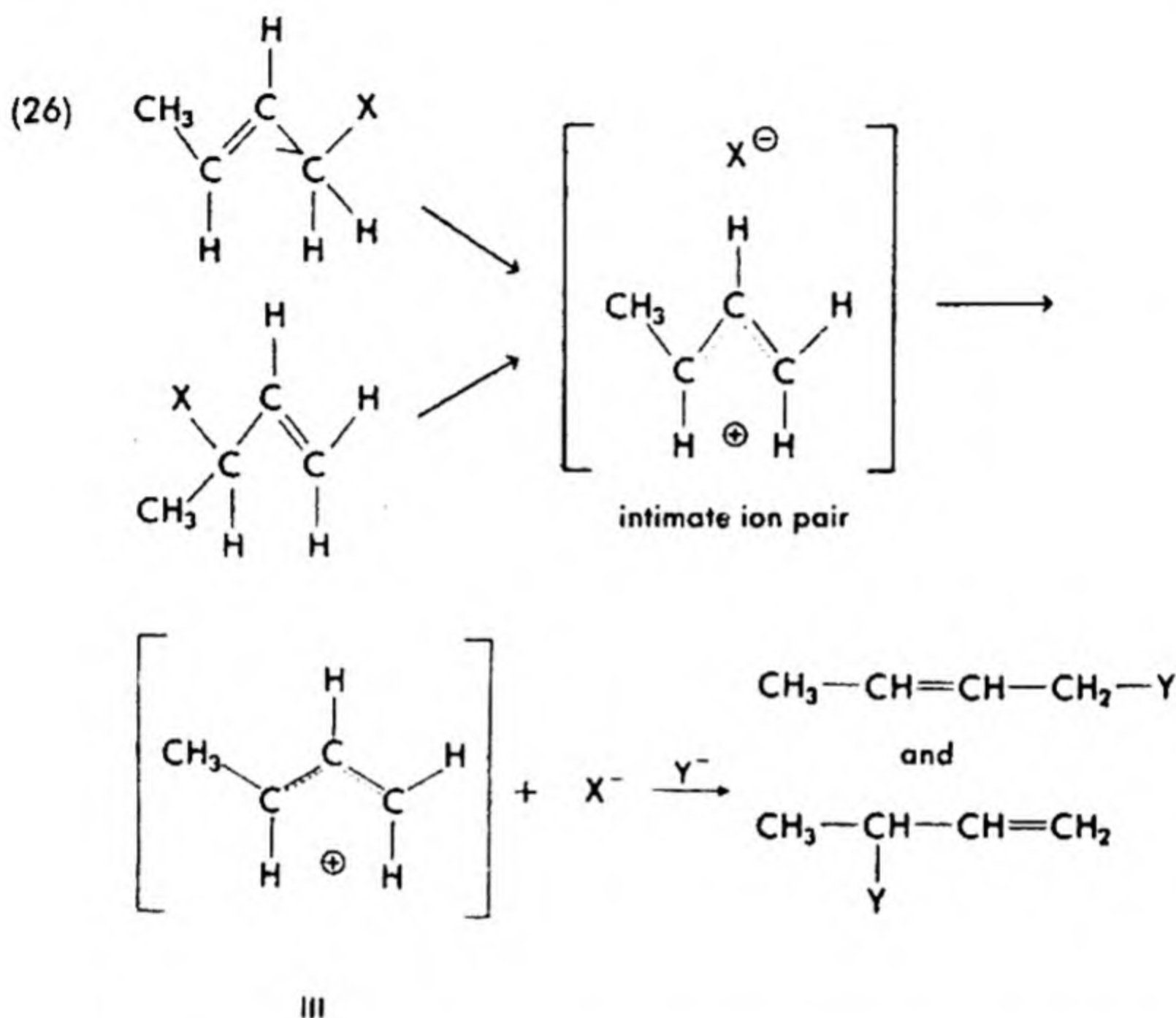


trans-crotyl chloride methyl crotyl ether



α -methylallyl chloride methyl α -methylallyl ether

On the other hand, reaction of a substituted allylic compound, such as crotyl chloride or α -methylallyl chloride, by the carbonium ion process goes through the intermediate, III, which is common to reactions of both isomers.



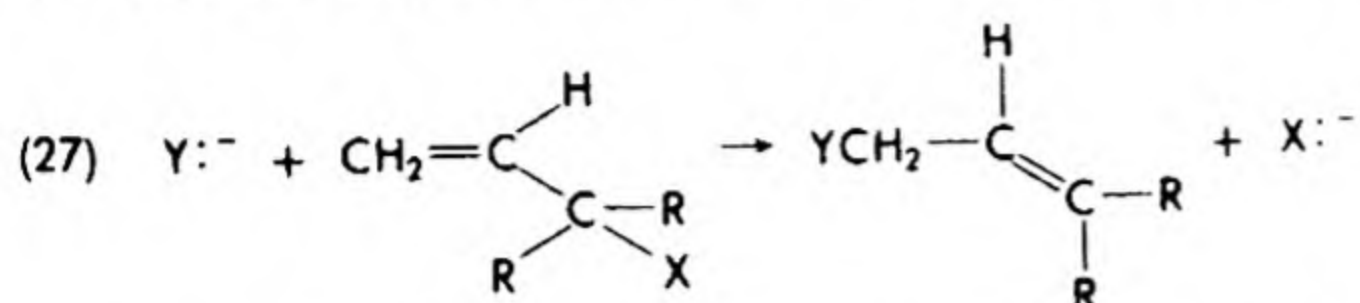
Since the intermediate III no longer contains the group X and is the same regardless of the starting isomer, the same ratio of products is obtained from either isomer, where X^- is *any* leaving group that permits reaction by the S_N1 mechanism. The transition state for the reaction with Y^- does, however, contain the nucleophile (generally solvent); hence the product ratio varies somewhat depending on Y^- .

Before the carbonium ion separates from its counter-ion, X^- , the intimate ion pair preceding III may collapse back to a covalent species. This is called *internal return*. Since the anion has "forgotten" its original position, it may return to either end of the allylic system to give a mixture of isomers of the starting material. In fact, chemists often study the properties of intimate ion pairs such as these by observing the rate of isomerization of the starting material.

Such rearrangements are called *allylic rearrangements*. *Rearrangements* are reactions which change the carbon skeleton or the point of attachment of a functional group or both.

In a few cases, *bimolecular* attack on allylic systems leads to rearrangements. These tend to occur when the nucleophile is large and when the

α -carbon atom is highly substituted. Such a reaction, called an abnormal bimolecular displacement reaction (symbol S_N2'), is outlined in eq. (27).



(6) *Competition between Direct Displacement and Carbonium Ion Processes in Reactions of Alkyl Halides.* The carbonium ion process is often a self-defeating one, as carbonium ions are generally not very selective in their reactions and tend to react with the solvent rather than with the desired nucleophile. This has no consequences except for configuration when the solvent is the conjugate acid of the nucleophile, for example, an alcohol with an alkoxide or a carboxylic acid with its salt, as the products are identical (see §12-1B(3)). It is, however, important in other cases. For example, treatment of an alkyl halide with sodium phenoxide in ethanol might give largely ethyl alkyl ether rather than the desired phenyl alkyl ether.

It is possible, in many cases, to control the mechanism of the reaction by suitable modification of reaction conditions. Note (eq. 9) that the rate of the direct displacement process depends upon the concentration of the nucleophile, whereas the rate of the carbonium ion process is independent of this. Increasing $[Y]$ therefore favors the direct displacement (but may also favor side reactions in which Y participates); decreasing $[Y]$ favors the carbonium ion process.

Solvent also plays an important role. The transition state for the ionization of an alkyl halide is a highly polar species, almost at the ion-pair stage, and is much more polar than the reactant alkyl halide. On the other hand, the reaction of an anion with a neutral molecule leads to a slight loss in polarity. Therefore, polar protic solvents like water, formic acid, and ethanol, which can partly neutralize charges and can stabilize anions by hydrogen bonding, favor carbonium ion processes (§12-1B(2)), whereas relatively nonpolar solvents, such as benzene, and dipolar aprotic solvents, such as acetone and dimethylformamide, favor direct displacement reactions.

In many cases the nucleophile is simply not nucleophilic enough to react with an alkyl halide, but can react with a carbonium ion. Under such circumstances, the formation of the carbonium ion may be catalyzed by Lewis acids such as silver ion, zinc chloride, or aluminum chloride.

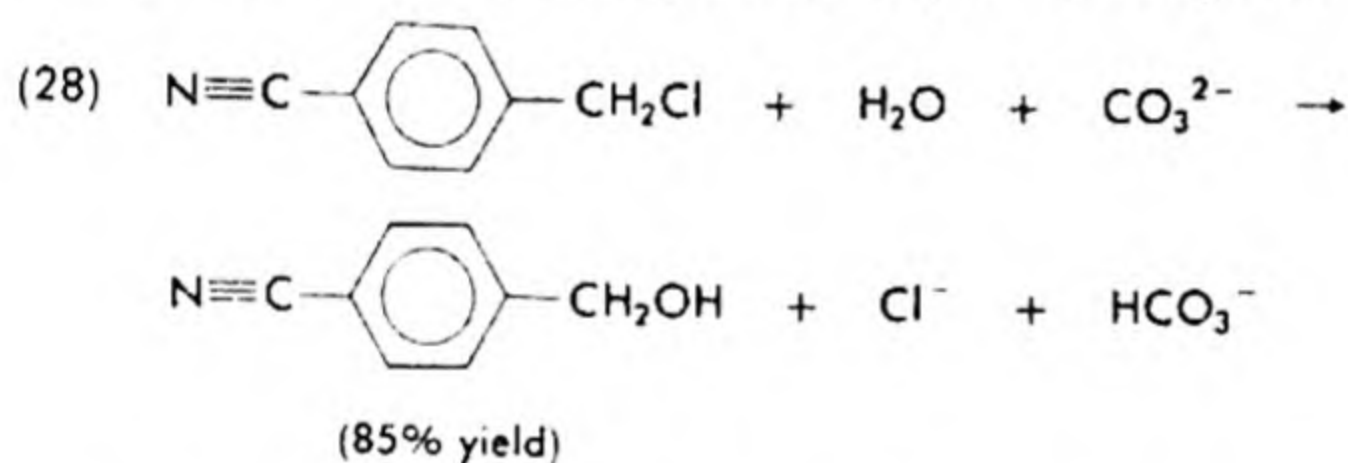
C. Typical Reactions of Alkyl Halides, Sulfates, and Sulfonates

We will now mention some specific nucleophilic displacements in which the common alkylating agents—alkyl halides $R-Cl$, $R-Br$, and $R-I$,

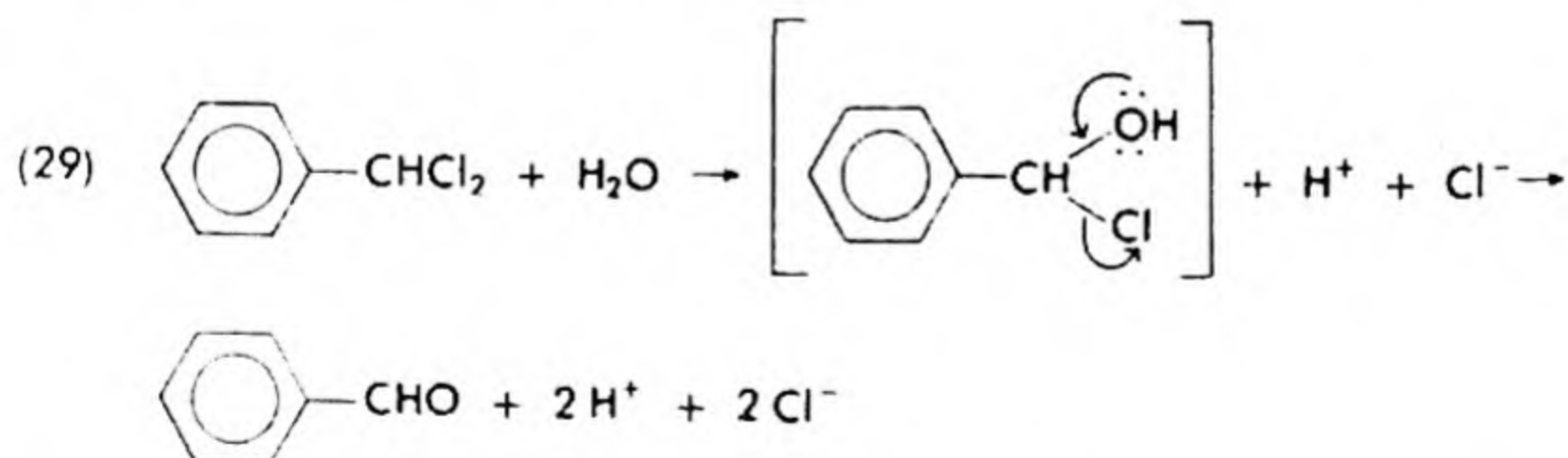
alkyl sulfonates $\text{ROS}-\text{R}$, and sulfates (methyl sulfate, $\text{CH}_3\text{OSO}_2\text{OCH}_3$,
 $\begin{array}{c} \text{O} \\ \uparrow \\ \text{ROS}-\text{R} \\ \downarrow \\ \text{O} \end{array}$
is most common) — are used. In all of these cases, there is initially a fairly large dipole, R^+X^- , so that attack by the electron-rich nucleophile at the carbon atom in the direct displacement process, or else ionization to R^+ and X^- , is facilitated. In addition, the anions Cl^- , Br^- , I^- , $-\text{OSO}_2\text{R}$, and $-\text{OSO}_2\text{OCH}_3$ are all relatively stable species.

One of the most thoroughly studied of the replacement reactions of halides is their conversion to hydroxy compounds. However, except for a few special cases, this reaction is of little importance in industry, since most hydroxy compounds are more economically produced from other sources. Commercial availability of many alcohols has made the reaction of minimum utility for laboratory syntheses as well. However, a few syntheses are important enough to be cited.

Ease of hydrolysis of a benzyl halide is illustrated by the preparation of *p*-cyanobenzyl alcohol by treatment of *p*-cyanobenzyl chloride with potassium carbonate solution. In this reaction, a halogen atom is more easily replaced than the cyano group is hydrolyzed.

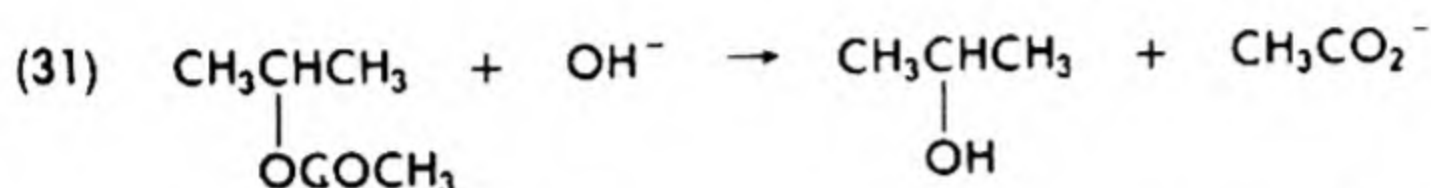
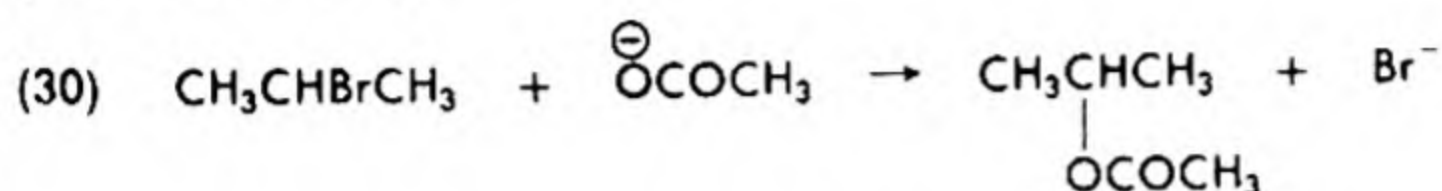


An industrial application of the reactivity of benzylic halides is the preparation of benzaldehyde from benzylidene chloride (eq. 29), obtained by dichlorination of toluene.

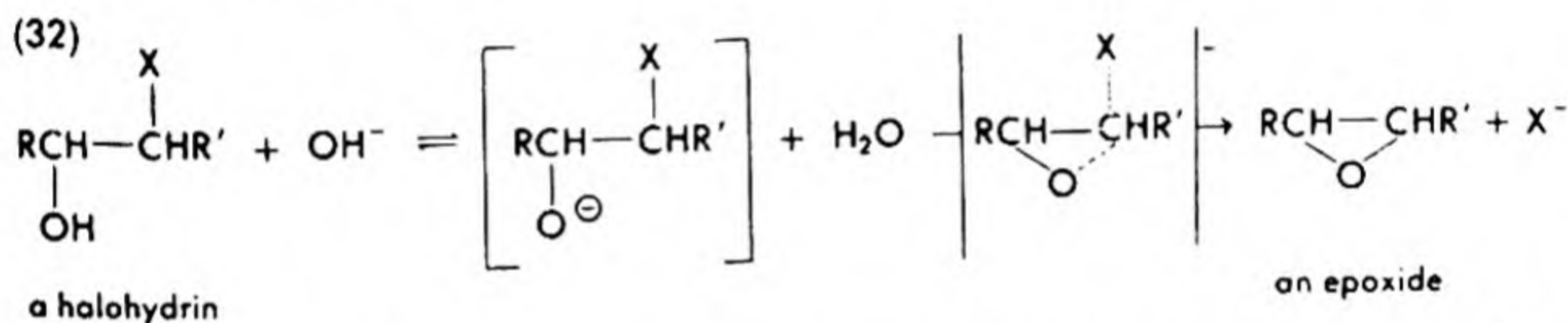


Certain halides form olefins to such a large extent in the presence of strong alkalis that their hydrolyses require special tricks, often involving mechanistic changes. One procedure utilizes a carbonium ion process with product acid neutralized by a mild or insoluble base, such as silver

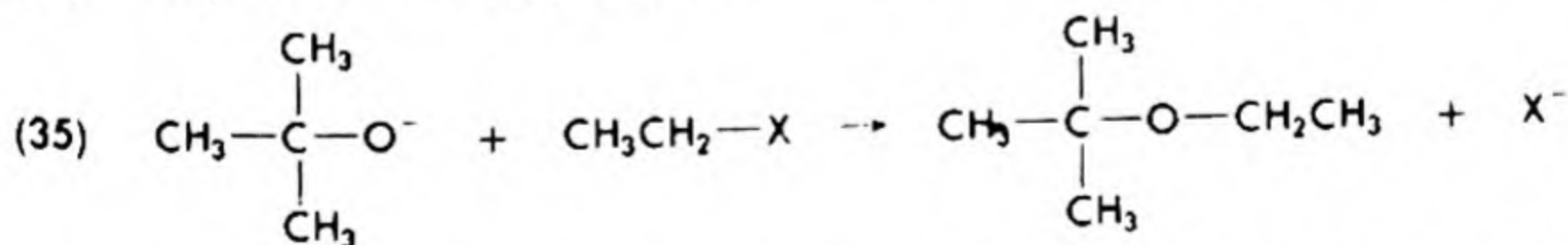
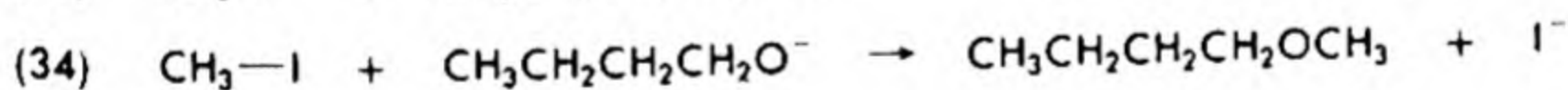
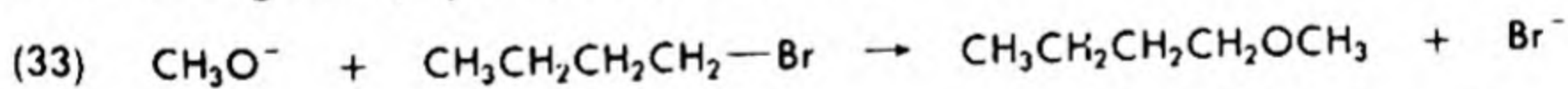
oxide, lead oxide, sodium bicarbonate, or calcium carbonate. Another approach is to form acetates by direct displacement with sodium acetate and then hydrolyze the ester with acid. This procedure is especially suitable when the product, such as an aldehyde, ketone, or hydroxy acid, is sensitive to alkali, or when other side reactions occur with strong bases (see Table 13-1).



Vicinal dihalides tend to produce epoxides (eq. 32) when hydrolyzed by bases even as strong as sodium carbonate, because of the sensitivity of the intermediate halohydrins to dehydrohalogenation. Weak or insoluble bases, such as those mentioned above, are therefore used to effect hydrolysis of vicinal halides.



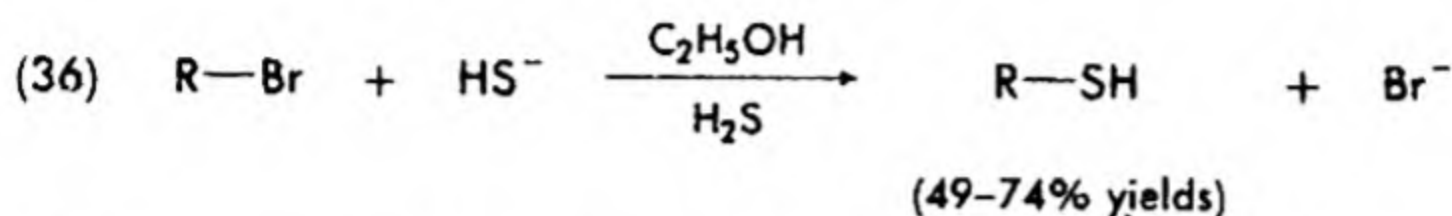
Preparation of unsymmetrical ethers by the sulfuric acid method (§12-2 ff.) is generally impractical, since too many by-products are obtained. The *Williamson synthesis* is therefore widely used for the preparation of these ethers. The ether can usually be made by either combination of reagents (eqs. 33 and 34). However, when one of the halides is



sensitive, its use as one of the reagents is avoided (eq. 35). For tertiary alkyl ethers, however, the Williamson method gives such poor yields that other methods are more suitable.

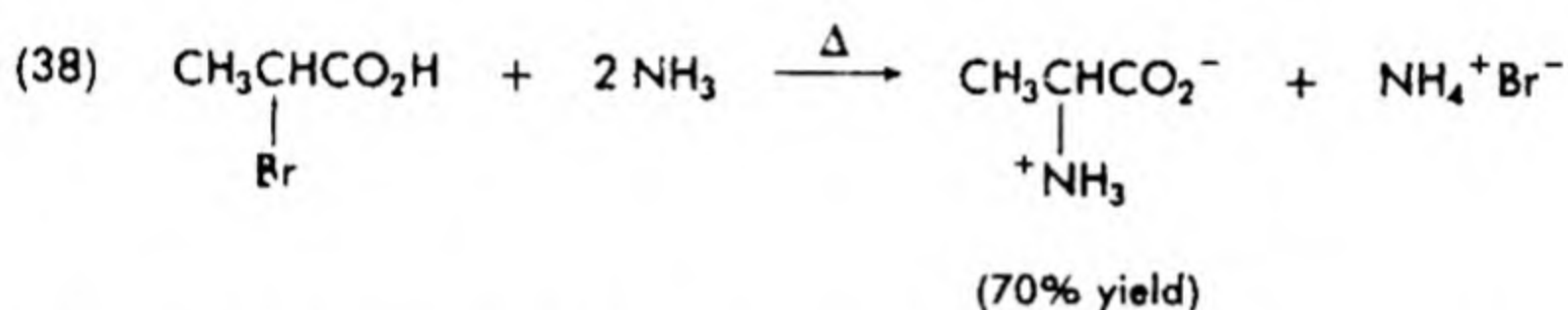
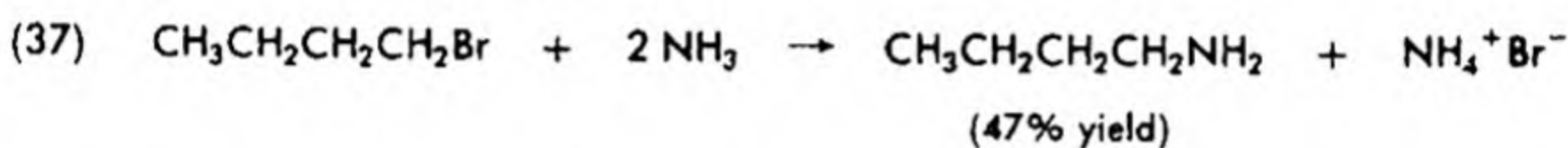
The unreactivity of aryl halides and ease of preparation of phenoxides from phenols makes it necessary to prepare alkyl aryl ethers by use of the alkyl halide or sulfate and phenoxide.

Mercaptans, thioaldehydes, thioketones, and sulfides can be prepared by reactions very similar to those used to prepare the corresponding oxygen compounds from halides. A mercaptan is prepared by treating a halide or sulfate with an alkali bisulfide in alcohol with excess hydrogen sulfide. Good yields of normal and secondary alkyl mercaptans (eq. (36), $R = \text{CH}_3$ through C_9H_{19}) have been obtained.

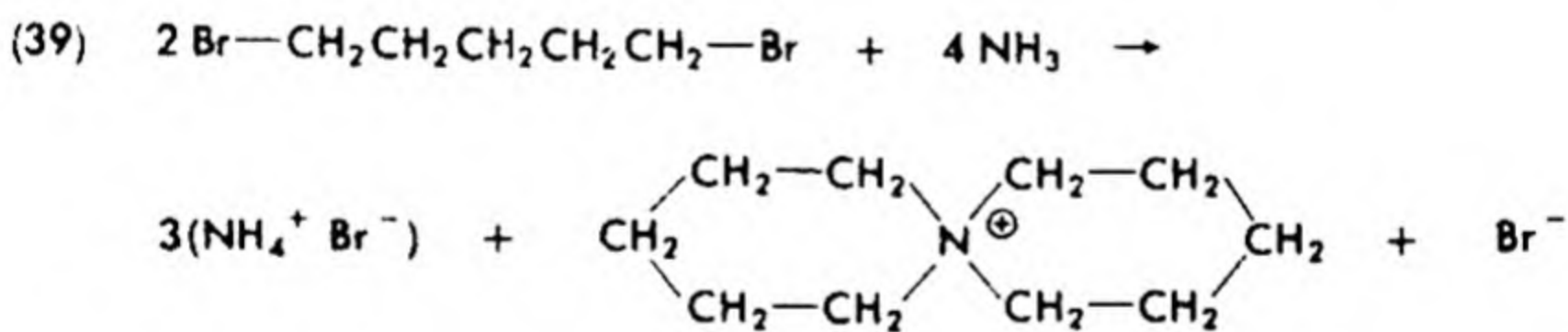


Sulfides are readily prepared by the Williamson method. Symmetrical sulfides are also prepared directly by the action of sodium sulfide on a halide or sulfate.

The *Hofmann synthesis of amines* is a very useful reaction of halides. Typical examples follow.

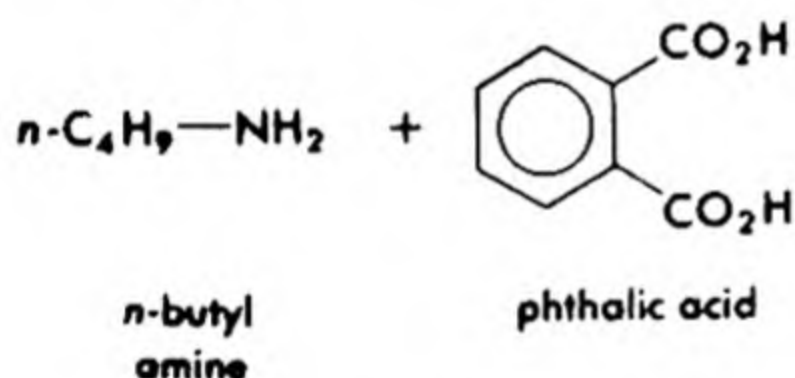
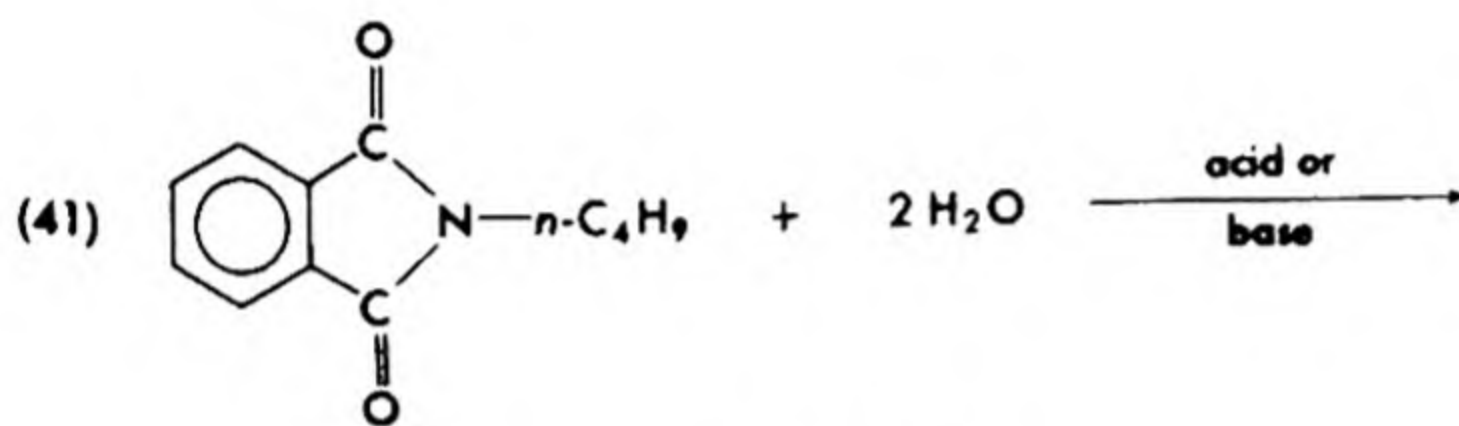
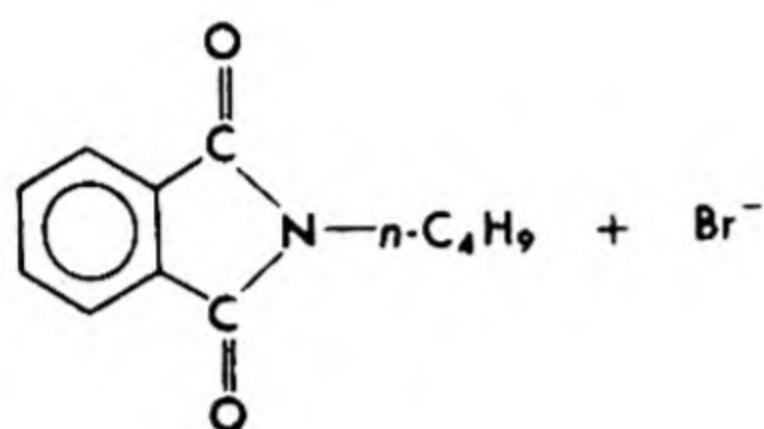
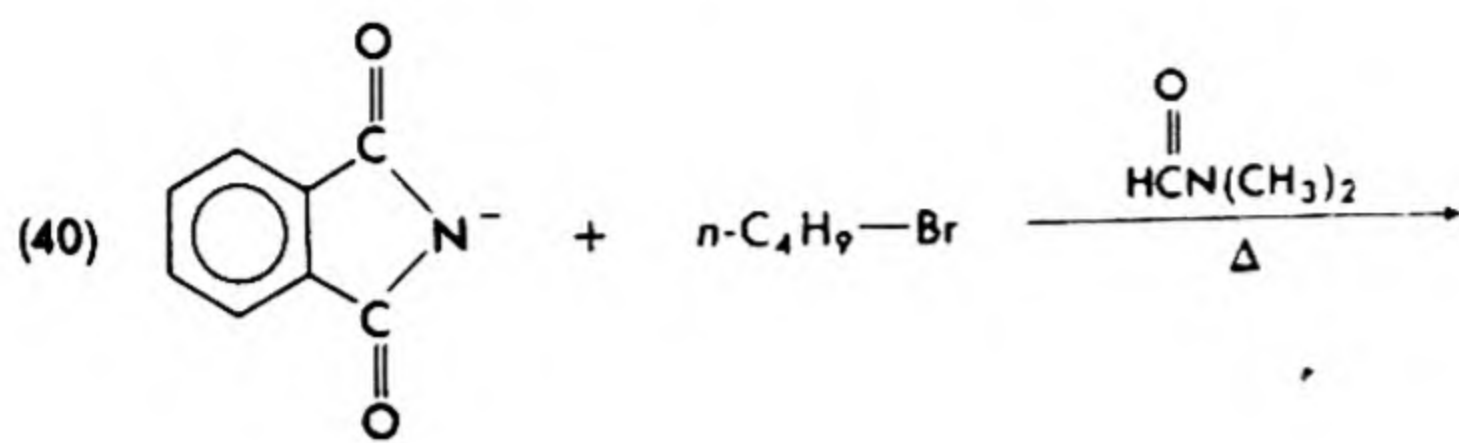


When ring formation is easy, cyclic amines or ammonium compounds are formed.



Because polyalkylation invariably results in the formation of mixtures during the Hofmann synthesis of amines, means of preparing primary amines by more selective reactions have been sought. One of the more successful of these is the *Gabriel synthesis* as recently modified, using dimethylformamide as the solvent. Phthalimide with potassium carbonate, or potassium phthalimide, is heated with an alkyl halide in the solvent to give good yields of *N*-alkylphthalimides in relatively short time. These are then readily hydrolyzed to the primary amines (eq. 41). The overall yield of *n*-butylamine in eqs. (40) and (41) is 67%.

Many other examples of substitution reactions are given in the problems following §12-1D and through the text.

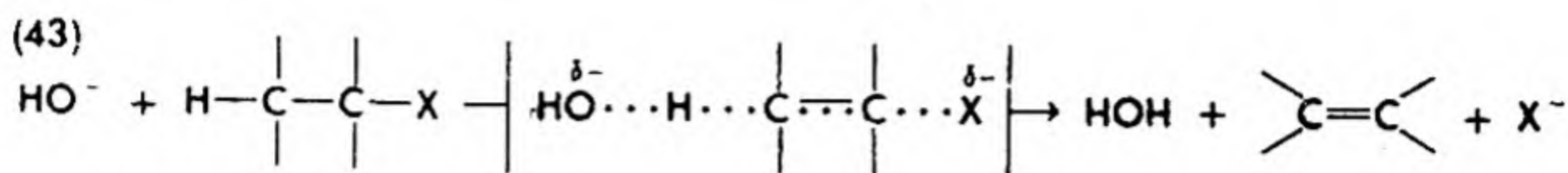
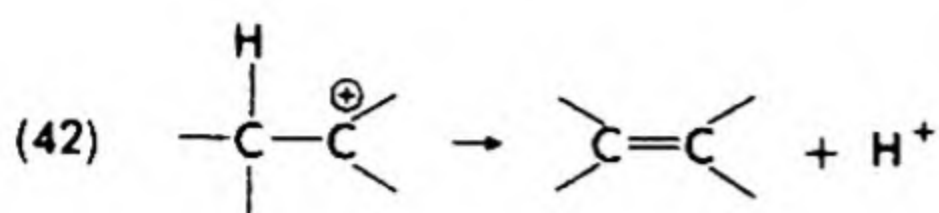


(one of these as its salt)

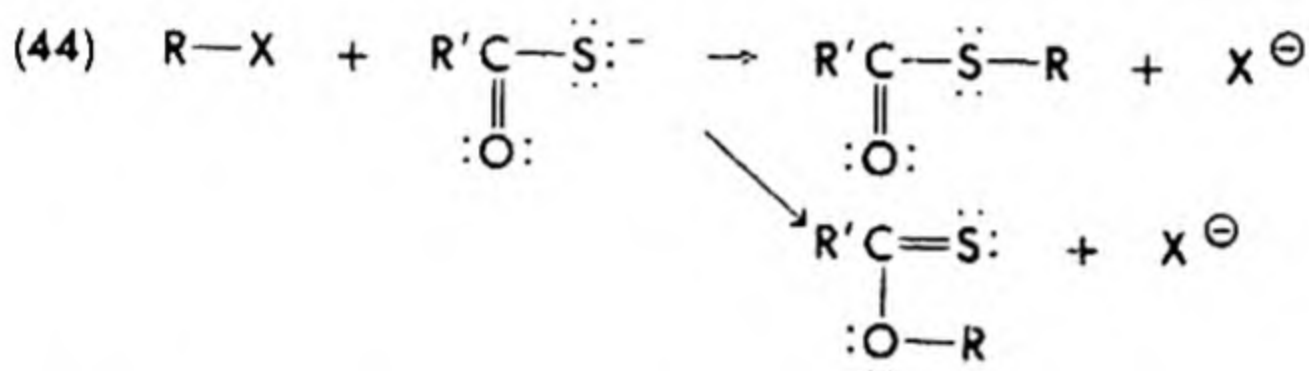
D. Side Reactions

The most common and most general side reaction of halides and sulfates during replacement reactions is loss of elements of hydrogen halide or sulfuric acid with olefin formation. This *elimination* reaction is most prominent in the use of tertiary halides and sulfates, but may also occur extensively in reactions of primary and secondary compounds.

This side reaction is often, but not always, related to the carbonium ion mechanism. Carbonium ions may stabilize themselves not only by coordination with a nucleophile, but also by loss of a proton to give an olefin (eq. 42). Alternatively, the basic reagent may attack the alkyl halide at the beta hydrogen, resulting in removal of a hydrogen ion simultaneously with loss of the halide ion (eq. 43). (See §13-1C). In many cases, olefin formation becomes the major reaction.

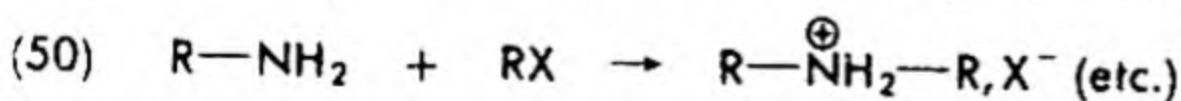
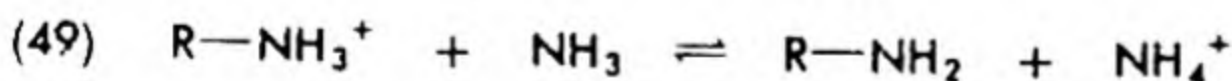
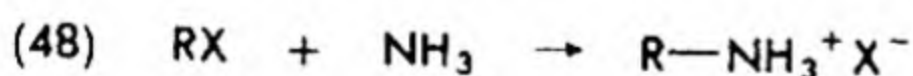
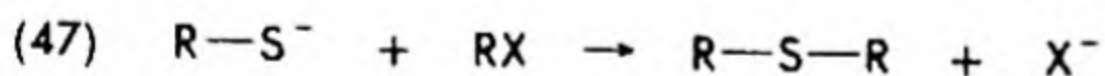
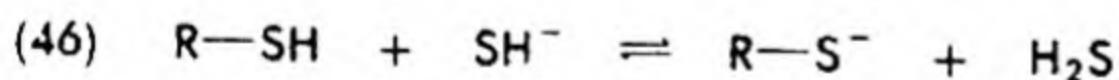
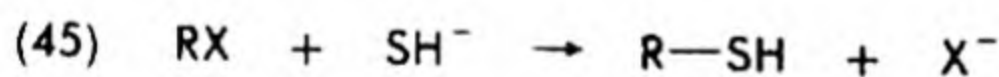


Another common side reaction involves multiatomic nucleophiles which have more than one nucleophilic center, called *ambident ions*. Mixed products result from attachment of the nucleophile to the alkyl group by different atoms. An example is the formation of nitrites as well as nitro compounds from sodium nitrite and halides discussed earlier (§12-1B(3)). Another is formation of both thiol esters and thione esters by reaction of salts of thioacids with alkyl halides or sulfates.



Alkylation of alternative positions cannot always be avoided. However, the desired product can be favored by proper choice of the alkali metal salt or the silver salt as reagent and to some extent by choice of solvent system.

A third kind of side reaction is polyalkylation. This can occur whenever the initial product of a replacement reacts with the reagent base to form a new nucleophile. Two such occurrences are illustrated in eqs. (45) through (50).



Polyalkylation can be minimized by using a large excess of the nucleophilic reagent. In the case of the mercaptan synthesis, addition of hydrogen sulfide to minimize the effect of the reaction represented in eq. (46) also helps. Similarly, in the preparation of alcohols from halides, the use of water as solvent decreases the relative importance of formation of alkoxides and consequent ether formation.

SUPPLEMENTARY READINGS

- Bunton, C. A., *Nucleophilic Substitution at a Saturated Carbon Atom*, Elsevier, Amsterdam, 1963.
- DeWolfe, R. H., and W. G. Young, "Substitution and Rearrangement Reactions of Allylic Compounds," *Chem. Revs.*, **56**, 753 (1956).
- Gould, E. S., *Mechanism and Structure in Organic Chemistry*, Henry Holt, New York, 1959, pp. 250-286, 296-298.
- Hine, J., *Physical Organic Chemistry*, 2nd Ed., McGraw-Hill, New York, 1962, pp. 123-185.
- Ingold, C. K., *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y. 1953, Chapter VII, "Mechanisms of Nucleophilic Substitution at Saturated Carbon."
- Patai, S., Ed., *Chemistry of the Alkenes*, Interscience, 1965, Chapter 11.
- Streitwieser, A., *Solvolytic Displacement Reactions*, McGraw-Hill, New York, 1963.
- Thornton, E. R., *Solvolysis Mechanisms*, Ronald Press, New York, 1964.

QUESTIONS AND PROBLEMS

- Name and describe briefly, giving equations, two mechanisms by which polar organic compounds can undergo displacement.
- Show how the hydrocarbon group may favor one or the other of the mechanisms in the reaction of alkyl halides. Give examples with structural formulas showing intramolecular forces for both.
- Write the structural formula for the appropriate halide or sulfate and the formula of the nucleophile necessary to prepare each of the following in good yield.

a. isopropyl alcohol	g. diisopropyl sulfide
b. <i>n</i> -butyl isocyanide	h. <i>N</i> - <i>n</i> -decylphthalimide
c. <i>n</i> -propyl mercaptan	i. 3-nitropentane
d. ethyl isocyanate	j. ethyl phenyl sulfide
e. butyronitrile	k. tetramethylammonium iodide
f. ethyl 2°-butyl ether	l. phenetole
- Write equations for the reactions that occur between the following compounds. Use structural formulas for organic compounds. Indicate essential conditions.

a. <i>n</i> -butyl iodide and excess ammonia	g. 2-chloro-2-methylbutane and 6 <i>N</i> sodium hydroxide
b. isobutyl bromide and silver cyanide	h. methyl sulfate and sodium phenoxide
c. methyl sulfate, <i>tertiary</i> -butyl alcohol, and sodium hydroxide	i. 2-chloroethanol and sodium iodide in acetone
d. <i>sec</i> -butyl chloride and sodium cyanide	j. sodium chloroacetate and sodium 2,4-dichlorophenoxide (what is the commercial name of this product?)
e. ethyl sulfate and sodium valerate	
f. 1-chloro-2-pentene and silver nitrate in 2-propanol	

5. How do silver oxide, lead oxide, sodium bicarbonate, and calcium carbonate act to provide better yields of hydroxy compounds from certain halides?

6. Show how the following compounds can be prepared in good yield from the suggested starting materials. Outline form may be used, but structural formulas for organic compounds and essential special conditions must be shown.

- | | |
|--|---|
| a. 1-nitropentane from <i>n</i> -amyl bromide | g. <i>tert</i> -butylamine from isobutane |
| b. ethyl butyl ether from <i>n</i> -butyl bromide and ethanol | h. dicyanomethane from methane |
| c. phenylnitromethane from toluene | i. <i>equatorial</i> -1-iodo- <i>trans</i> -decalin from <i>axial</i> -1-bromo- <i>trans</i> -decalin |
| d. methylisobutylamine from methyl iodide and isobutyl bromide | j. malonic acid from sodium chloroacetate |
| e. cyclopentyl cyanide from cyclopentane | k. methyl sulfate from carbon monoxide |
| f. ethylene glycol from ethylene chloride | l. <i>n</i> -propylamine from ethyl bromide |
| | m. isoamylamine from isoamyl bromide and phthalic anhydride |

7. Show how the following compounds can be prepared in good yield beginning with *n*-octyl bromide and inorganic reagents. Indicate essential conditions. Use structural formulas for organic compounds.

- | | |
|--|------------------------------|
| a. <i>n</i> -octyl <i>n</i> -pelargonate | d. di- <i>n</i> -octylamine |
| b. <i>n</i> -octylamine | e. <i>n</i> -octyl mercaptan |
| c. <i>n</i> -nonylamine | |

8. Discuss side reactions which may be important in the hydrolysis of the following compounds. Tell why the side reaction may occur to a large extent. Show how this can be avoided. Explain why the method of avoiding the side reaction is effective.

- | | |
|-------------------------------|-------------------------|
| a. <i>tert</i> -butyl bromide | c. 3-bromobutanoic acid |
| b. 1-chloro-2-propanol | |

9. Define or illustrate the following terms.

- | | |
|--------------------------|--------------------|
| a. direct displacement | e. rearrangement |
| b. allylic rearrangement | f. S_N1 reaction |
| c. carbonium ion | g. S_N2 reaction |
| d. internal return | |

12-2 NUCLEOPHILIC REPLACEMENTS IN ALCOHOLS AND ETHERS

The relative acid strengths of the hydrogen halides, of water, and of alcohols are a measure of the tendency of the H—Y bond to cleave ionically. By analogy one might guess that the carbon-oxygen bond in

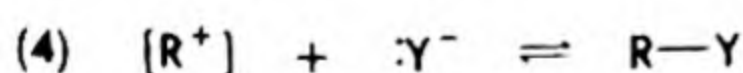
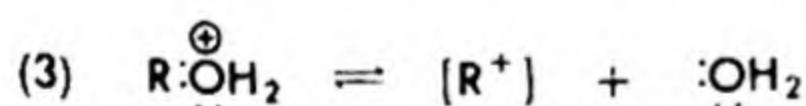
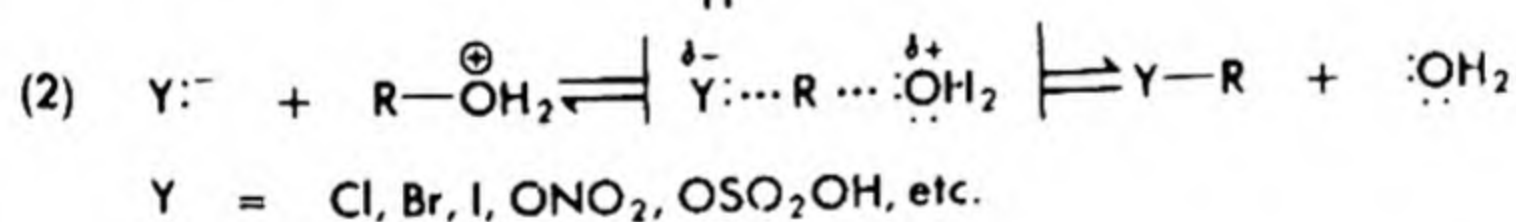
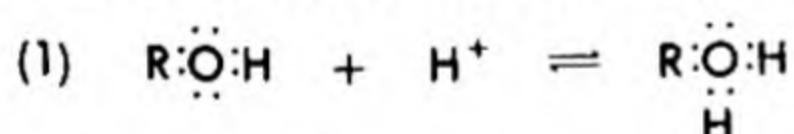
alcohols or in ethers would be more difficult to cleave than the carbon-halogen bond in alkyl halides. Hydroxy and alkoxy groups are, in fact, very poor leaving groups (see Table 12-1) so that C—O bonds in saturated and many unsaturated alcohols and ethers are stable in neutral or in basic solution. On the other hand, alkyloxonium ions (protonated alcohols) and dialkyloxonium ions (protonated ethers) are strong acids and might be expected as well to be good alkylating agents (alkyl donors). This is the case, for $\text{H}-\overset{+}{\text{O}}-\text{H}$ and $\text{R}-\overset{+}{\text{O}}-\text{H}$ are excellent leaving groups

(Table 12-1). For this reason, the reactions of alcohols and of ethers involving carbon-oxygen cleavage are conducted in the presence of acid catalysts. Under such conditions, strong bases (e.g., CN^- , SH^-) exist only as their inactive conjugate acids. Hence, only the weaker bases (I^- , Br^- , Cl^- , H_2O , ROH , RCOH) can be utilized as nucleophiles in oxonium

ion displacements.

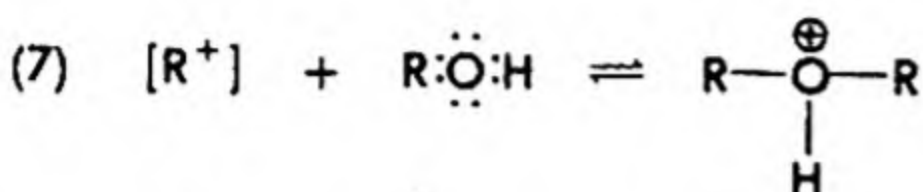
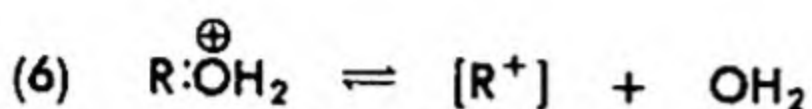
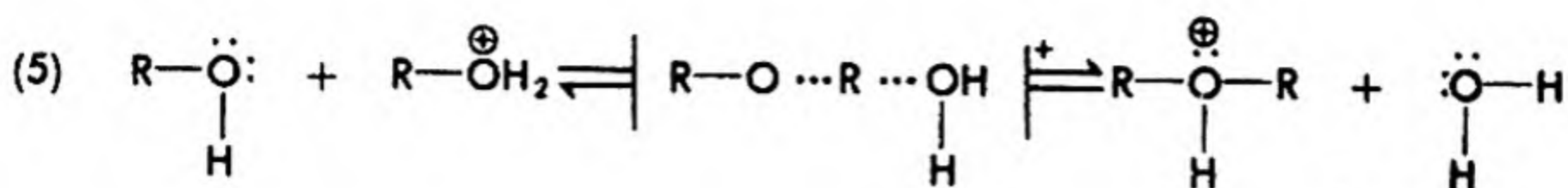
A. Mechanisms of Reactions

The oxonium salt initially formed by reaction of an alcohol or an ether with an acid exhibits reactions similar to those of alkyl halides. Strong electron withdrawal by the positive oxygen atom renders the adjoining carbon atom more susceptible both to nucleophilic attack in the direct displacement process and to carbonium ion formation. As with halides, either of the two mechanisms may operate.



The influence of alkyl groups on the mechanisms is identical to that of the same groups in reactions of alkyl halides. Reactivities are parallel. Conjugate acids of alkyl and benzyl alcohols are highly reactive. Phenols are inert (§12-1B(4)).

Ether formation and cleavage, two aspects of a reversible reaction, are essentially the same as the reactions represented in eqs. (1) through (4). These reactions, ether formation and cleavage, formation of alkyl halides and their hydrolysis, are reversible reactions. The position of the equilibrium (extent of reaction in either direction) is subject to control by the

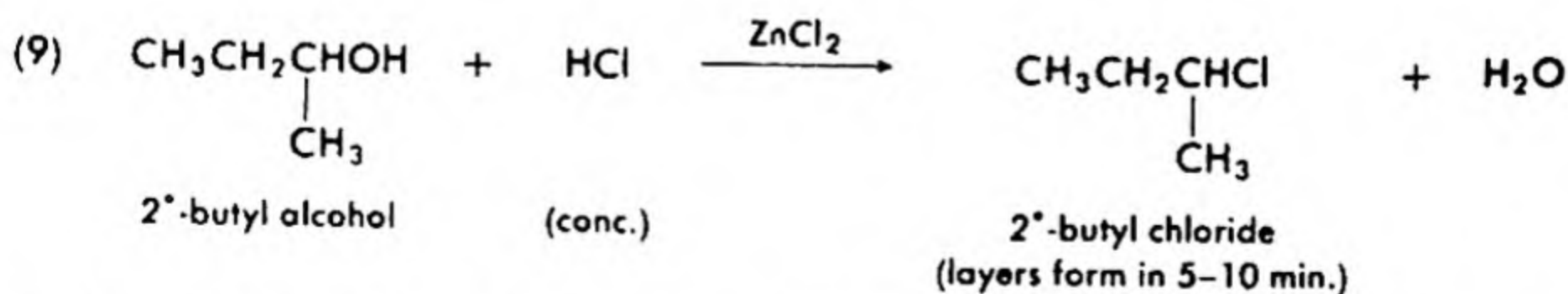
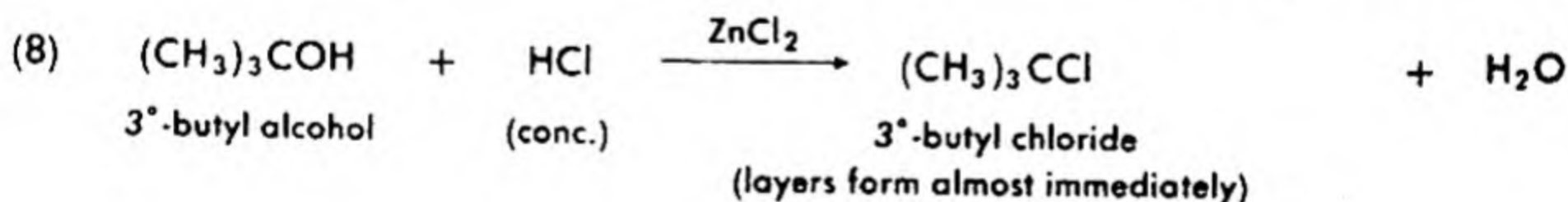


law of mass action. Thus, for example, ether formation and halide formation are favored by high concentrations of alcohol and of halide ion, respectively, and by a low concentration of water. The reactions are acid-catalyzed (eqs. 5-7) and are also subject to catalysis by alumina and by other Lewis acids.

B. The Reagents

The reaction rates are proportional to the concentration of protonated species; consequently, concentrated mineral acids are effective catalysts. Lewis acids such as boron trifluoride, hydrogen fluoride, and zinc chloride are often used as catalysts for reactions of alcohols and ethers.

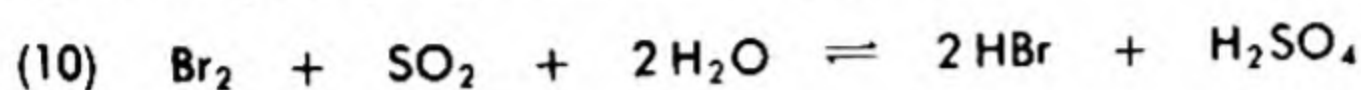
A mixture of concentrated hydrochloric acid and zinc chloride, called *Lucas' reagent*, is a very effective reagent for the conversion of alcohols to alkyl chlorides. This reagent has a much higher acidity than concentrated hydrochloric acid alone, presumably due to formation of a complex acid, H_2ZnCl_4 . *t*-Butyl alcohol forms *t*-butyl chloride in a few seconds at room temperature with this reagent; *sec*-butyl alcohol gives the chloride in 5-10 min., while *n*-butyl alcohol requires heating to react. This order of reactivity, $3^\circ > 2^\circ > 1^\circ$, makes it obvious that the reaction involves the carbonium ion mechanism for high reactivity. The reagent is used in



qualitative organic analysis to distinguish primary, secondary, and tertiary aliphatic alcohols by their reactivities.

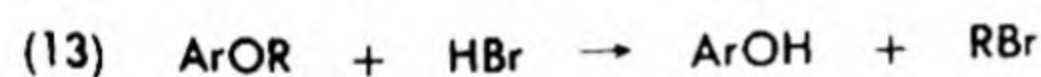
Rates of reaction of halogen acids with alcohols and ethers are in the order $\text{HI} > \text{HBr} > \text{HCl}$. Hydrogen fluoride is usually ineffective. This

order reflects the order of nucleophilicity of the halide ions present in aqueous or alcoholic solutions of the acids. A mixture of sulfuric acid and sodium bromide often replaces commercial hydrobromic acid, or the reagent may be prepared as in eq. (10).

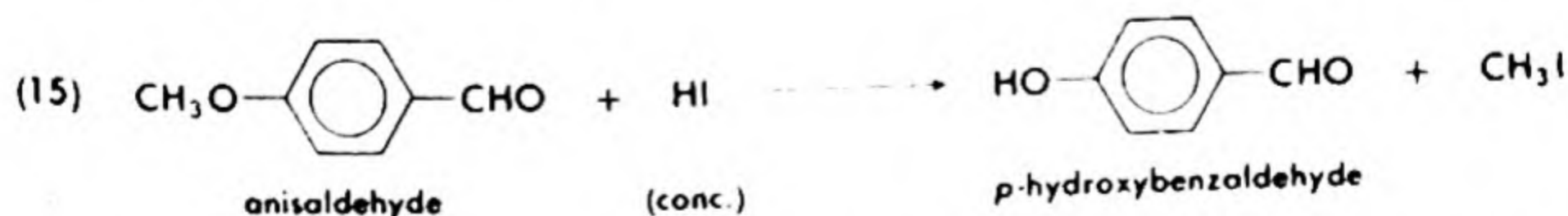


In either case, the sulfuric acid is a more effective protonating agent than hydrogen bromide. High yields of bromides are obtainable.

Although aqueous sulfuric acid or *p*-toluenesulfonic acid may be used to cleave ethers (reverse of eqs. 7-9), the reactions are often accompanied by side reaction. For practical purposes, these ethers are usually cleaved with hydrogen iodide or hydrogen bromide to give alkyl halides (e.g., eqs. 11 and 12). Aryl alkyl ethers are cleaved only at the alkyl-oxygen bonds (eq. 13), while diaryl ethers are inert. These reactions are particularly useful for identification purposes (the structure of the product halides gives the structure of the ether, ROR'), for quantitative analysis (*Zeisel method* for methoxy groups), or for regenerating a phenol which has been protected by an alkoxy group during some reaction at another site (e.g., oxidation) which would have degraded it. Because of the lack of

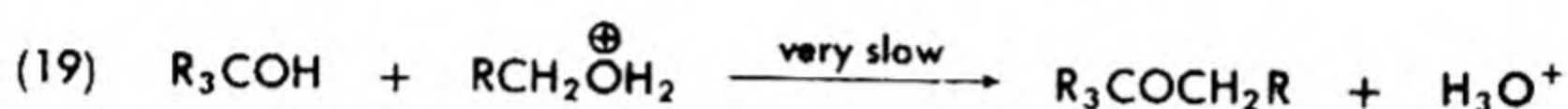
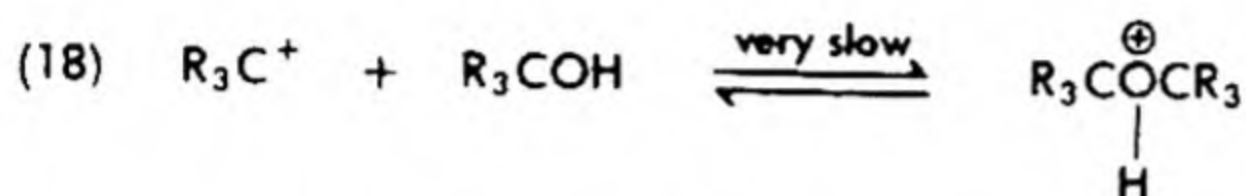
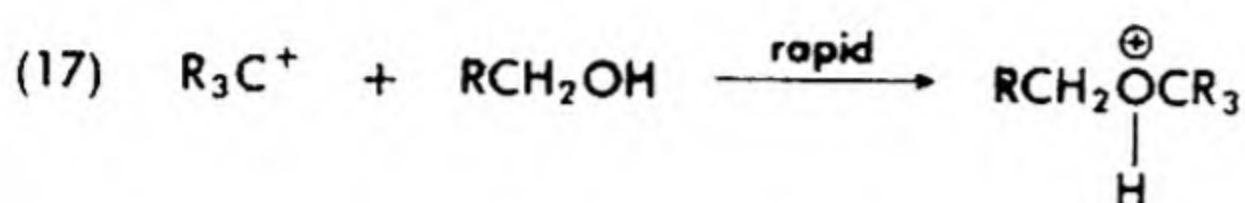
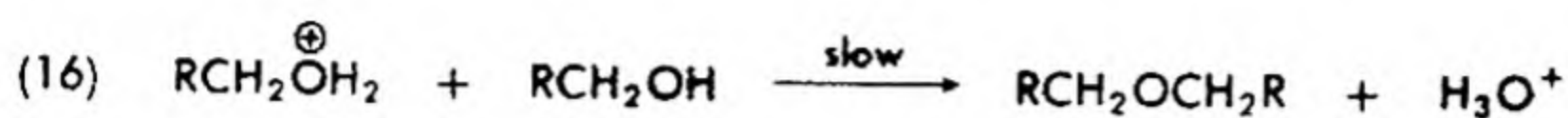


reactivity of aryl systems toward displacement (§12-1B(4)), diaryl ethers are not cleaved by acid-catalyzed procedures. Alkyl aryl ethers, on the other hand, are cleaved readily, and as many methyl aryl ethers occur in a variety of natural products, these serve as sources for the related phenols.



Mixed ethers with tertiary and primary alkyl radicals are usually best prepared by the dehydration method. Good yields result from the preferred coordination of the trialkylcarbonium ions with the molecules of primary alcohols present in excess. The rate-determining steps of the

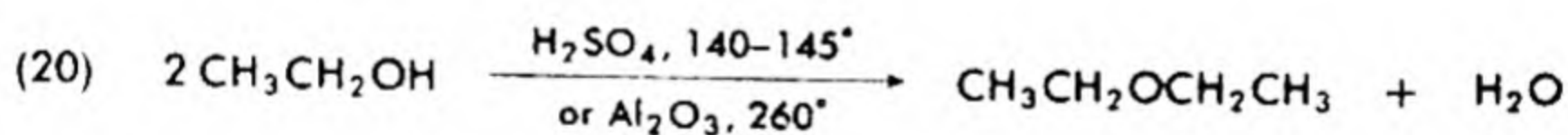
competitive reactions in eqs. (16), (18), and (19) are much slower than the rate-determining step in eq. (17). Hence the mixed ether is the preferred product.



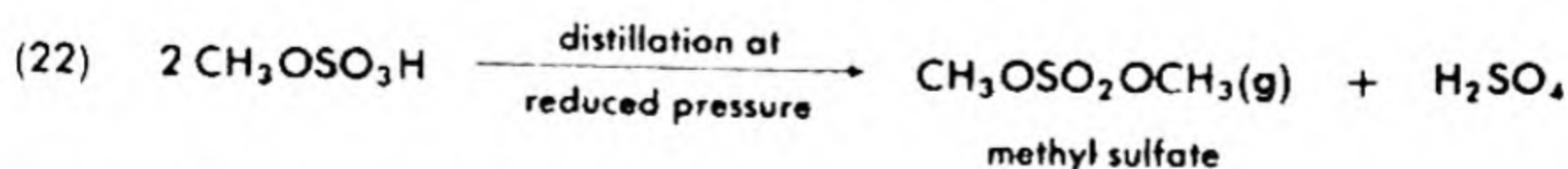
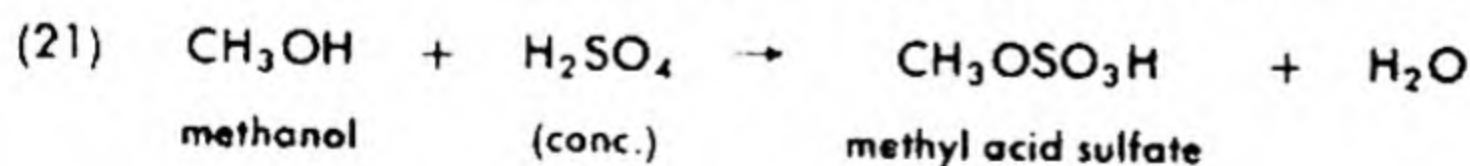
C. Typical Reactions

Diethyl ether has been prepared since its discovery in 1540 by Valerius Cordus by distillation of the ether from a mixture of sulfuric acid and ethanol. The distillation method is not suitable for ethers higher than dipropyl or for mixed ethers except those containing one tertiary and one primary alkyl radicals. The higher ethers have boiling points above those of their related alcohols, hence do not distill from the equilibrium mixture. Azeotropic distillation of the mixture with toluene or benzene to remove water has been used to adapt the method for these ethers.

Dehydration of alcohols over activated alumina occurs at relatively high temperatures, often without many of the side reactions inherent in the sulfuric acid method.



At more moderate temperatures, alkyl acid sulfates and lesser amounts of alkyl sulfates form by reactions between alcohols and concentrated sulfuric acid. Methyl sulfate can be produced by distillation of the acid sulfate under reduced pressure, a process which is used industrially.

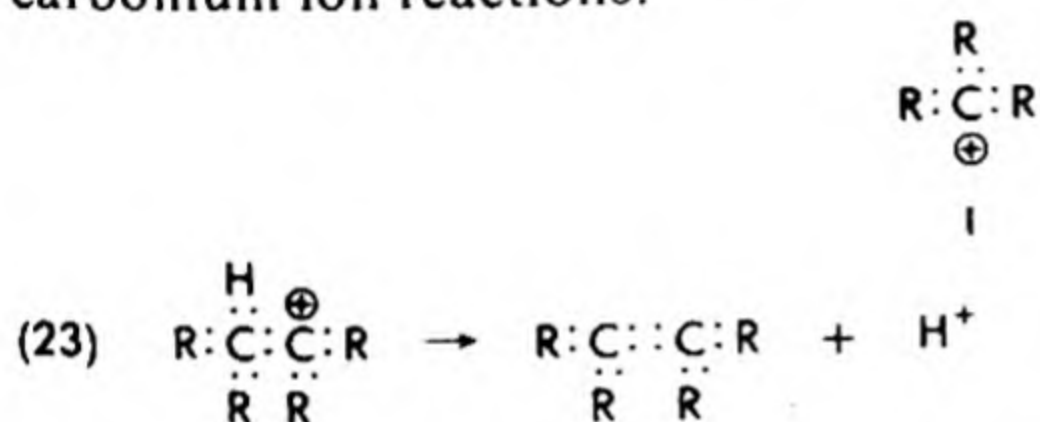


D. Side Reactions and Carbonium Ion Rearrangements

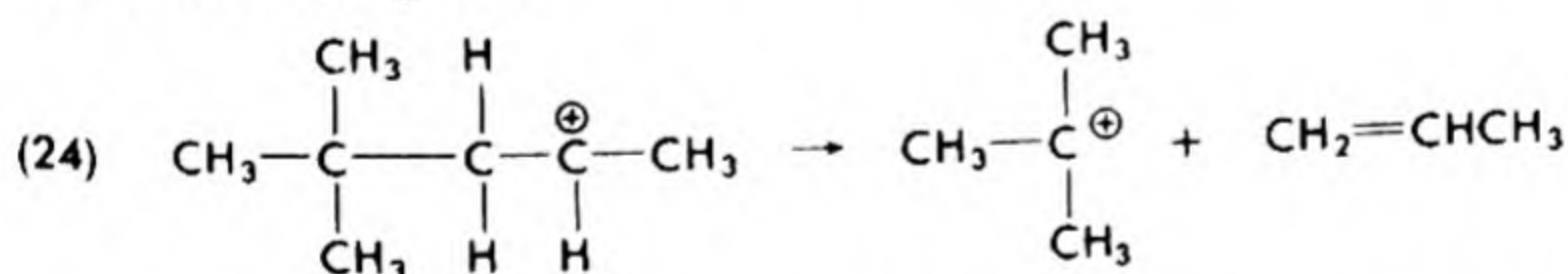
Probably the most general side reaction of compounds undergoing oxonium replacements is olefin-forming elimination. Whereas the olefins formed by elimination of hydrogen halides from alkyl halides cannot

ordinarily add nucleophilic reagents under the neutral or basic conditions utilized for such displacement reactions, they can react with the acid reagents used in oxonium replacements. These addition reactions give rise to secondary side reaction products.

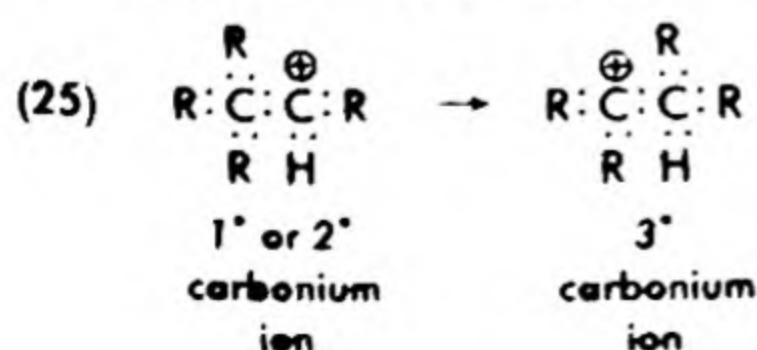
Molecular rearrangement often accompanies carbonium ion reactions. Carbonium ion intermediates are unstable species (except when highly resonance stabilized), the driving force for all of their reactions being the tendency to complete the electron octet around the carbon atom which has only six electrons in its valence shell (I). This can be done in a variety of ways. First, as we have seen, the carbonium ion can coordinate with a nucleophile, $Y:$, which donates an electron pair to share with the functional carbon atom. Another way to complete the octet is for one of the groups present on the functional carbon atom to lose a proton from its α carbon atom and to donate the remaining electron pair to the cationic center to give an olefin (eq. 23). Such olefin formation is very common in carbonium ion reactions.



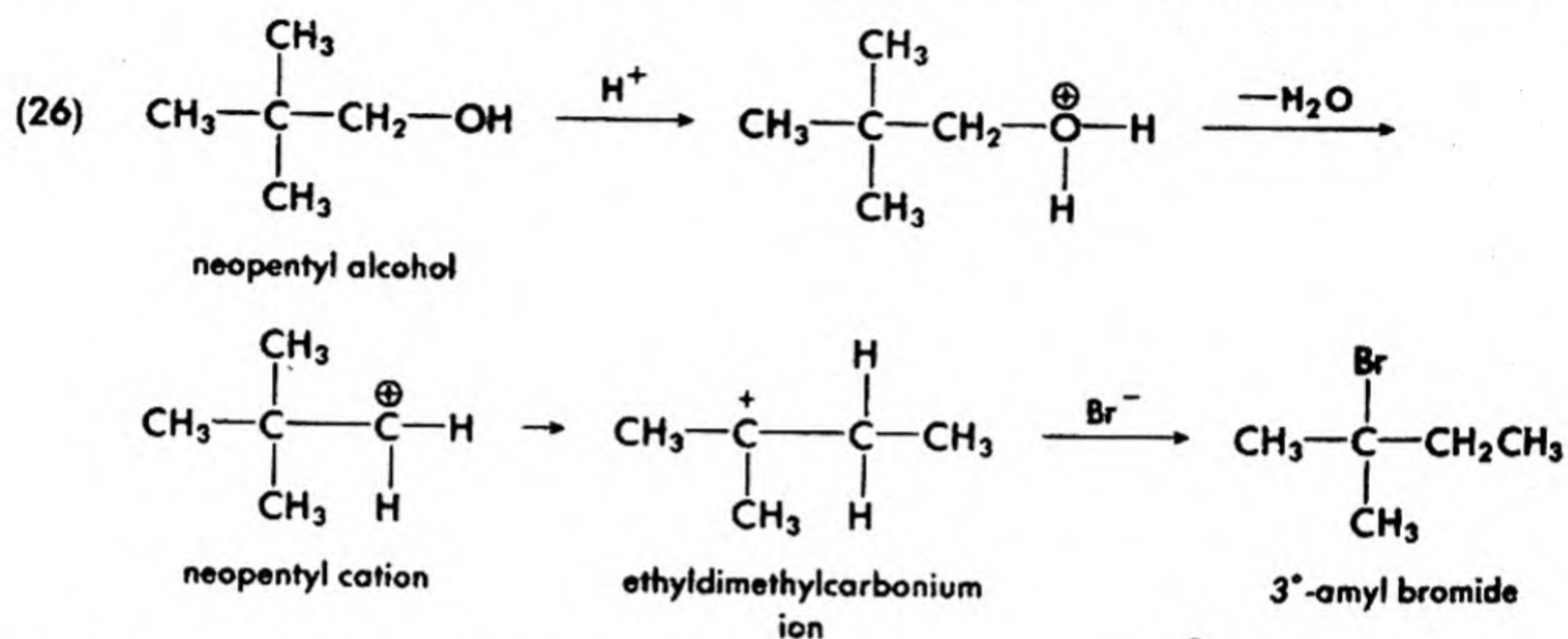
A variant of this reaction often occurs when, rather than a proton, a relatively stable carbonium ion is lost. This releases the double bond-forming electron pair to form an olefin. Such reactions are seen in acid-catalyzed cracking reactions. The driving force for the reaction in eq. (24) is the formation of the more stable tertiary carbonium ion from the less stable secondary ion.



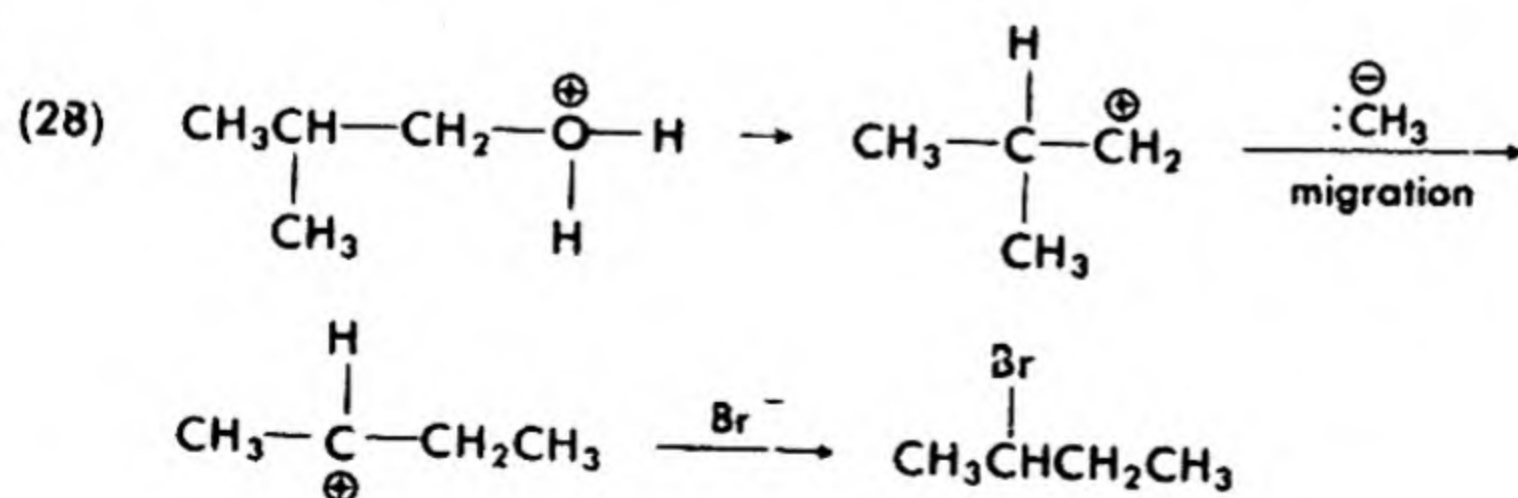
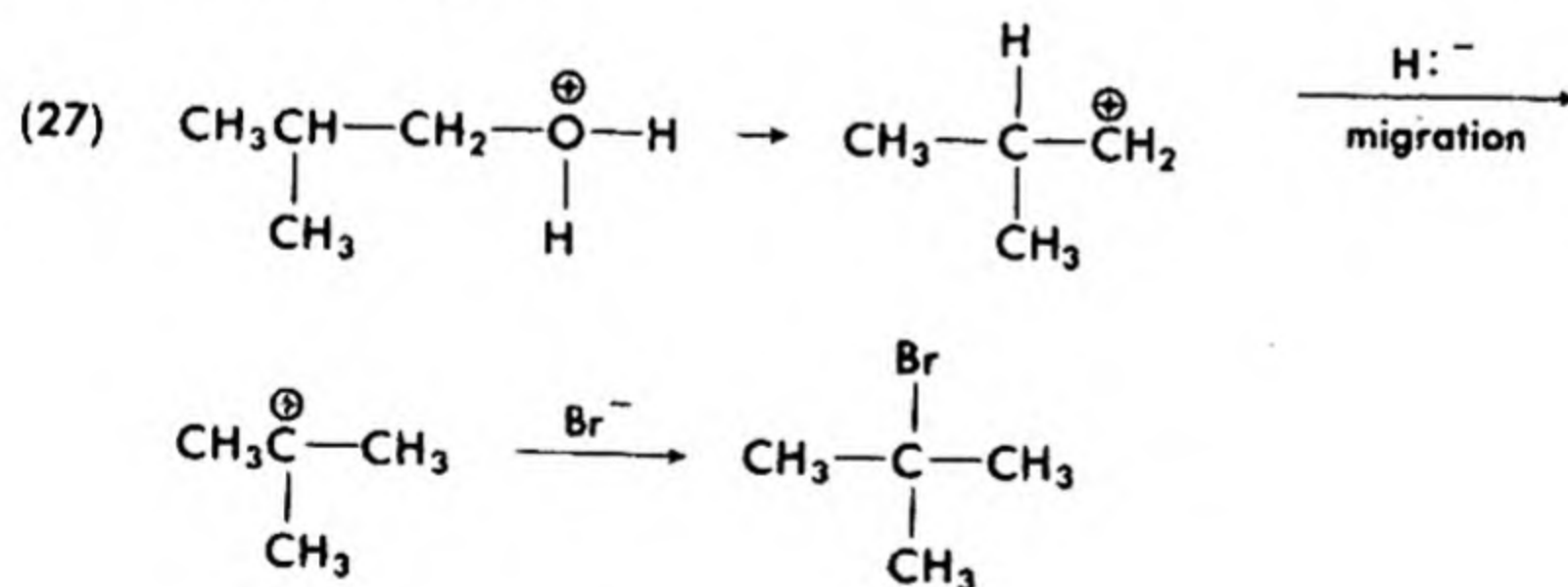
(1) *Wagner-Meerwein and Pinacol Rearrangements.* A third way in which the carbonium carbon atom may complete its octet is to take a group with its electron pair from a neighboring carbon atom (generally, but not always, the next one) to form a new carbonium ion. This new carbonium ion may now coordinate with a nucleophile, eliminate to an olefin, or



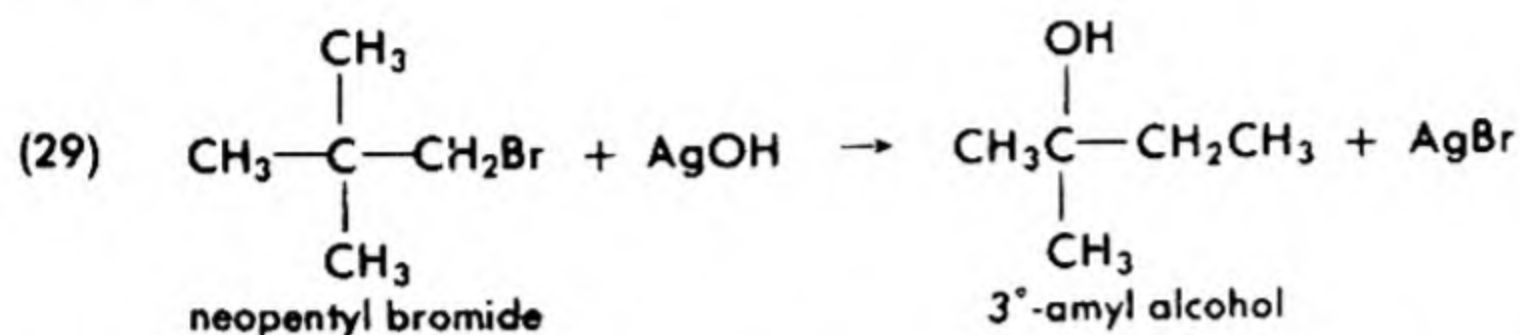
rearrange further. These rearrangements are not uncommon and always occur when a *neo* (or tetrasubstituted) carbon atom adjoins the functional carbon atom and that atom is primary or secondary. Thus neopentyl alcohol on treatment with hydrogen bromide gives only *tert*-amyl bromide. The driving force for this rearrangement is the formation of the stable tertiary carbonium ion from the less stable primary (or secondary) one. Both carbanion migration and hydride ion (H^-) migration occur.



Thus, isobutyl alcohol on treatment with hydrogen bromide gives some *tert*-butyl and some *sec*-butyl bromide along with the principal product, isobutyl bromide (eqs. 27 and 28). The extent of rearrangement depends upon the relative stability and the lifetime of the carbonium ion. If the original carbonium ion is captured rapidly by a nucleophile, the chance of its rearrangement is less than when it is formed under conditions where its lifetime is longer.

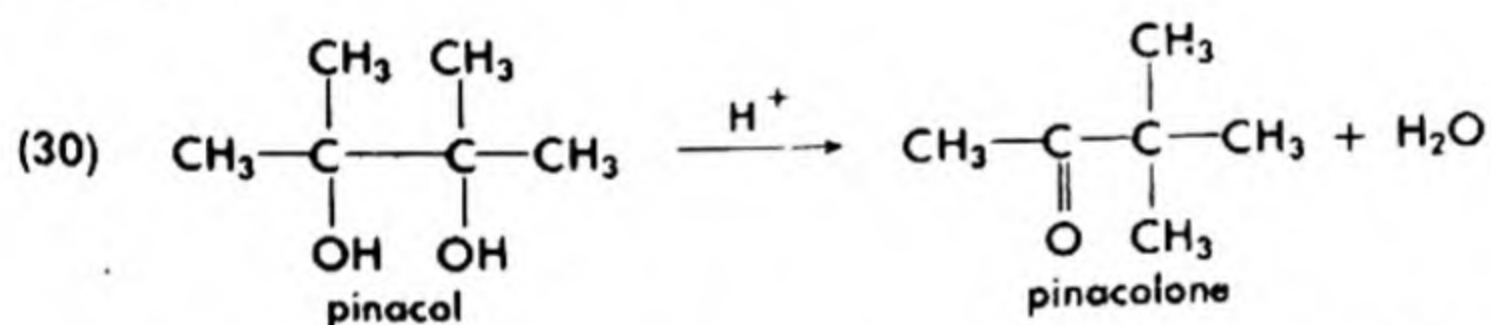


Carbonium ion reactions of halides also may involve rearrangements. Thus treatment of neopentyl bromide with silver hydroxide gives *tert*-amyl alcohol (eq. 29). The rearrangement path is similar to that described in outline (26).

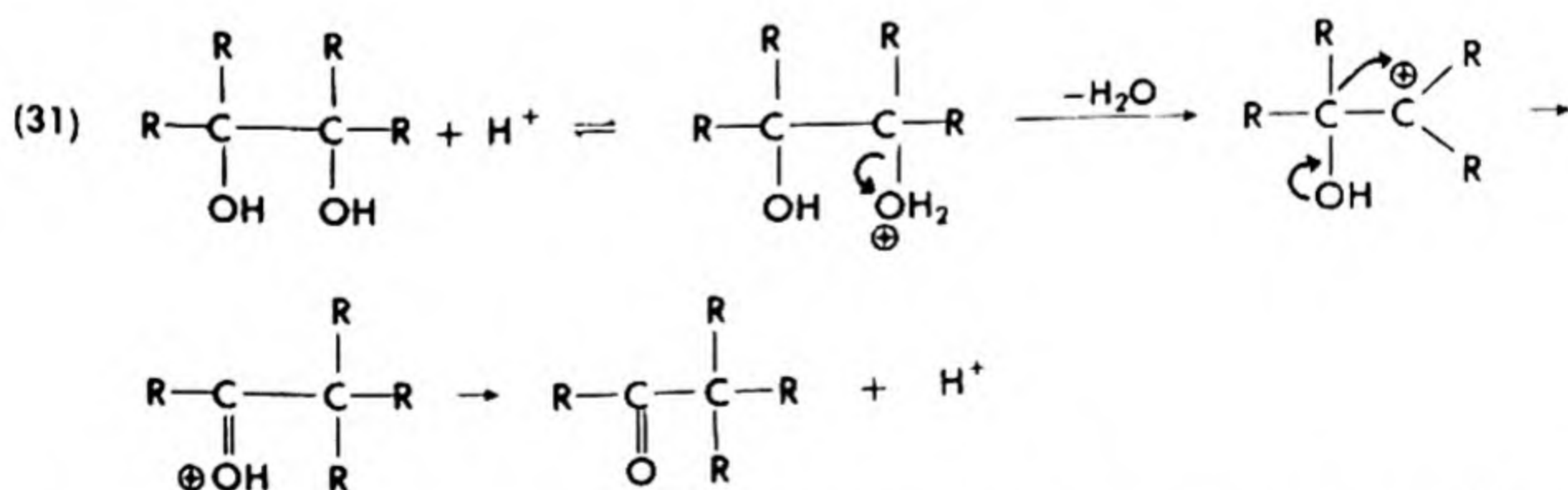


Although most displacement reactions we will discuss in our study of organic chemistry do not involve skeletal rearrangements, reactions that involve the generation of a sextet of electrons on an atom (carbon, nitrogen, or oxygen) often lead to group migrations such as have been described, and these represent an important and common system of rearrangement reactions. When simple 1,2-migration of groups occurs, as in the preceding cases, the rearrangement is called a *Wagner-Meerwein rearrangement*.

The *pinacol rearrangement* is a reaction of vicinal glycols, R_2COHR_2 , COH , and is named after the compound first observed to rearrange thus (eq 30).



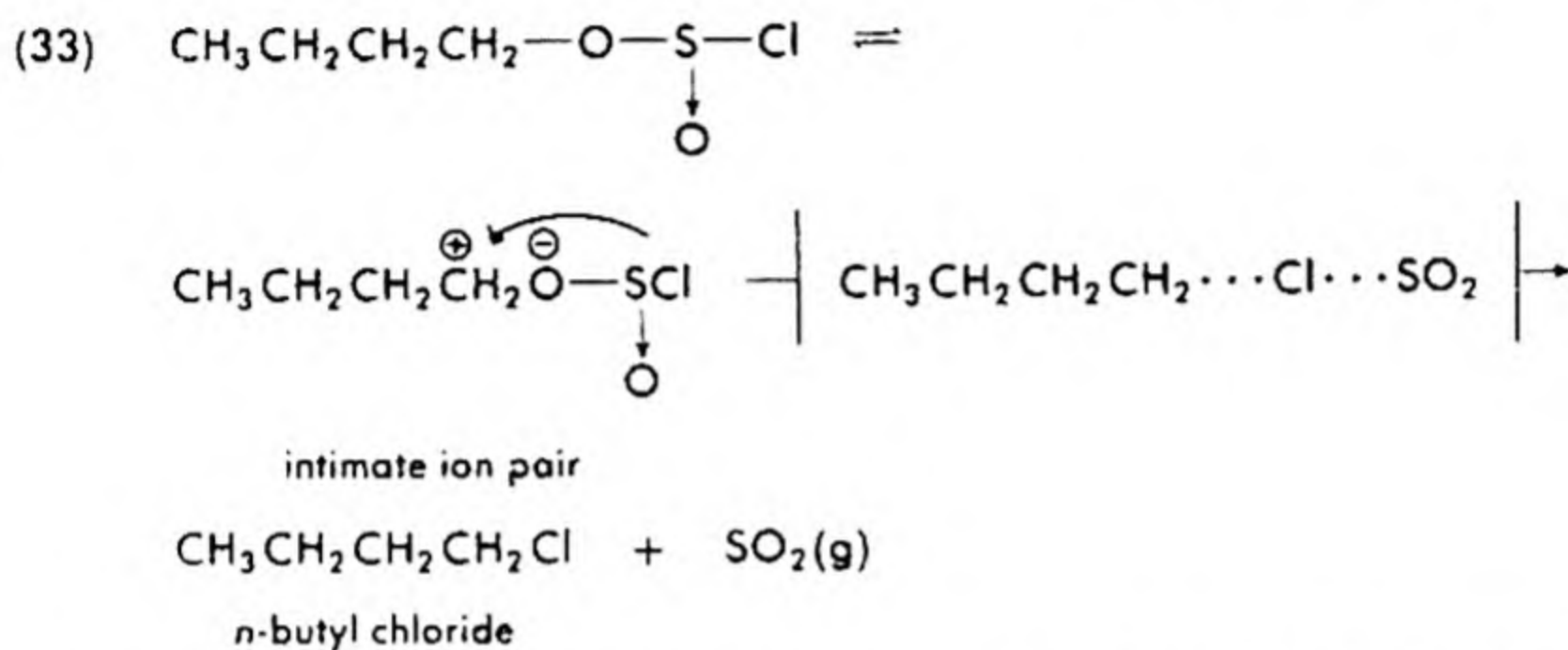
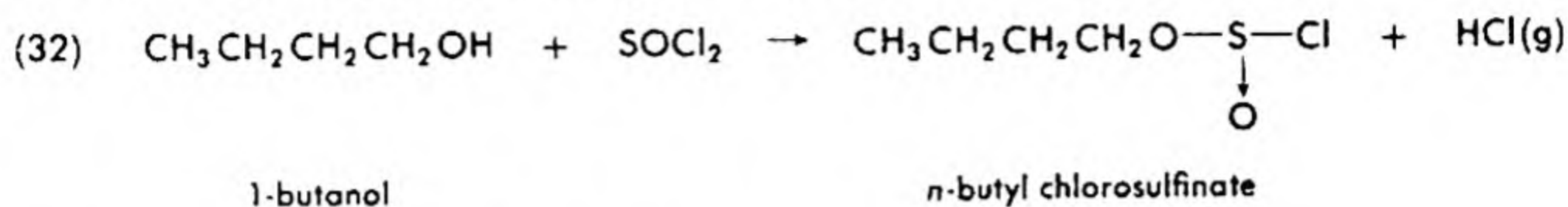
The mechanism is similar to that of the Wagner-Meerwein rearrangement.



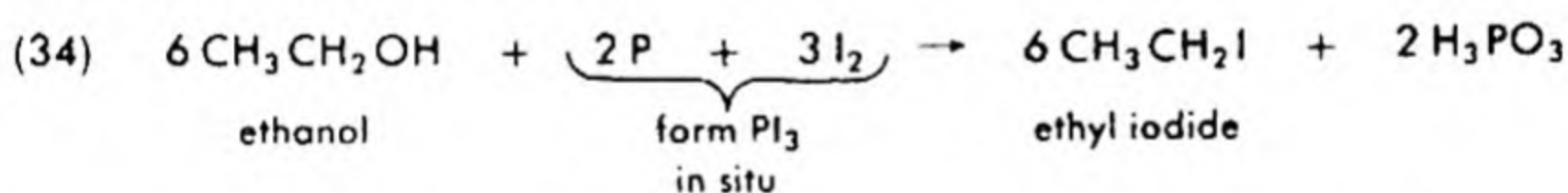
The pinacol rearrangement is quite general for glycols in which all four groups, R, are alkyl or aryl groups and becomes more difficult the more hydrogen atoms there are on the carbinol groups.

(2) *Alkyl Halide Formation with Inorganic Halides*. Internal return was mentioned, §12-1B(5), as participating in some allylic rearrangements,

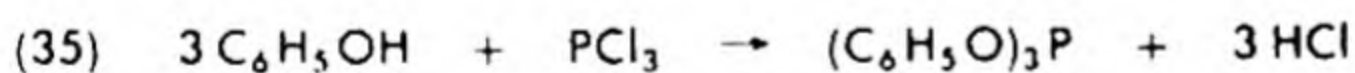
which involve a change in the point of attachment of an anionic group on an allylic carbon chain. Internal return also is involved in the formation of alkyl halides from alcohols and inorganic acid halides via alkyl chloroesters of phosphorus and sulfur acids. The essential rearrangement occurs on the inorganic group in this process (eq. 33).



The reactions with phosphorus halides, PCl_3 , PCl_5 , PBr_3 , and PI_3 , follow similar pathways. These reactions make easier the preparation of primary alkyl halides that are available from primary alcohols only upon more drastic treatment with hydrohalogen acids. However, skeletal rearrangements may occur, as carbonium ion intermediates are involved.



Phenols proceed only to the ester-formation stage, since aryl cations fail to form.



QUESTIONS AND PROBLEMS

1. Describe and explain the effects of hydrocarbon groups on compounds undergoing the following reactions.

- | | |
|--|---|
| a. replacement of hydroxy group by halogen | c. preparation of an ether by dehydration |
| b. cleavage of an ether | |

2. Tell whether the following can be done satisfactorily and explain why. If a more effective reagent is needed to bring about the desired transformation, tell what the reagent is.

a. preparation of an aromatic halide by treating a phenol with Lucas' reagent.

b. preparation of an aliphatic halide by treating a primary alcohol with dilute hydrochloric acid

c. cleavage of an aliphatic ether using concentrated hydrobromic acid

3. Write equations for the reactions that occur when the following compounds are mixed. Indicate essential special conditions. Use structural formulas for organic compounds.

a. 2°-butyl alcohol and hydrochloric acid

b. *n*-propyl alcohol and sulfuric acid ($\frac{1}{3}$ mole) at 140°

c. 1,1,2,2-tetraphenylethane-1,2-diol and hydrochloric acid

d. 3,3-diethyl-2-pentanol and concentrated sulfuric acid

e. 2,2-dimethyl-3-chloropentane and aqueous sodium hydroxide

f. neopentyl bromide and sodium sulfide

4. Show how the following compounds can be prepared in good yield from the suggested starting materials. Use structural formulas for organic compounds and indicate essential conditions.

a. *n*-amyl bromide from *n*-amyl alcohol

b. 2°-butyl bromide from the appropriate alcohol

c. di-*n*-propyl ether from the appropriate alcohol

d. 2,7-dimethyloctane from isoamyl alcohol

e. allyl mercaptan from allyl alcohol

f. ethylacetylene from ethanol and acetylene

g. *n*-butyl isocyanide from *n*-butyl alcohol

h. 3,4-dihydroxybenzaldehyde diacetate from veratraldehyde (3,4-dimethoxybenzaldehyde)

5. Describe the side reactions encountered in the preparation of *n*-butyl bromide from *n*-butyl alcohol by the use of sulfuric acid and sodium bromide. Write structural formulas for the organic products of these side reactions.

6. In the preparation of isobutyl bromide by a method analogous to that in Question 5 for the preparation of *n*-butyl bromide, what side reactions can be expected without counterparts in the preparation of the *normal* bromide? Write structural formulas for the products of these side reactions. Indicate how they be minimized.

7. An ether was cleaved to give isobutyl iodide and methyl iodide. Write the probable formula of the original ether. How certain can one be of the structure of the group that gave the isobutyl iodide? Why?

8. What products might you anticipate from the reaction of methyl-*tert*-butylcarbinol with hydrogen bromide?

9. Write equations to illustrate the following terms.

a. 1,2-shift b. Wagner-Meerwein rearrangement

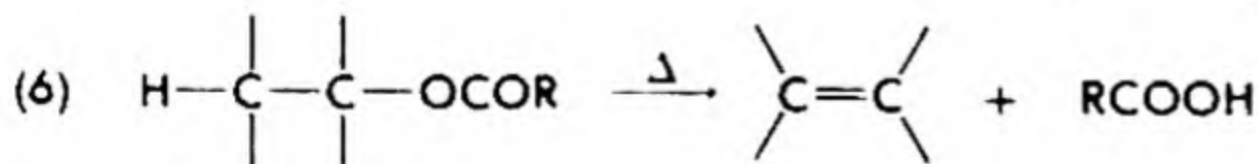
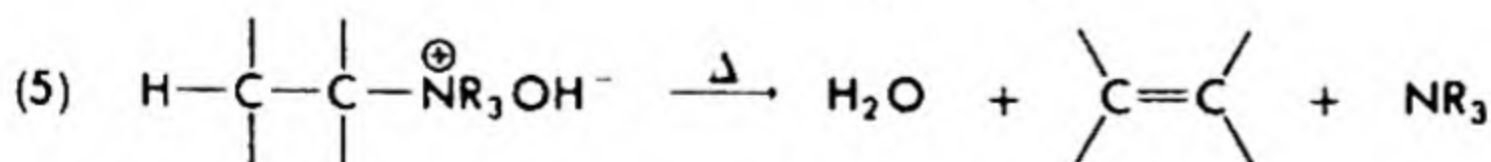
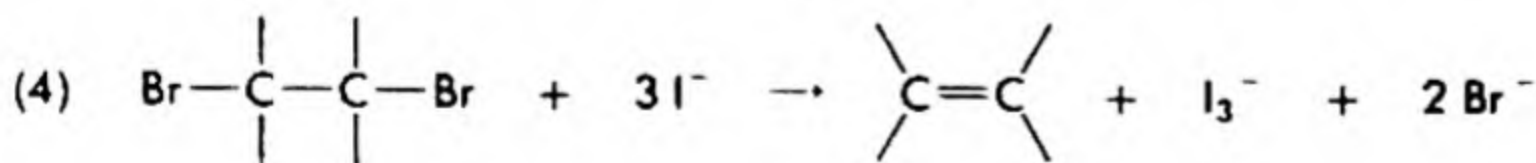
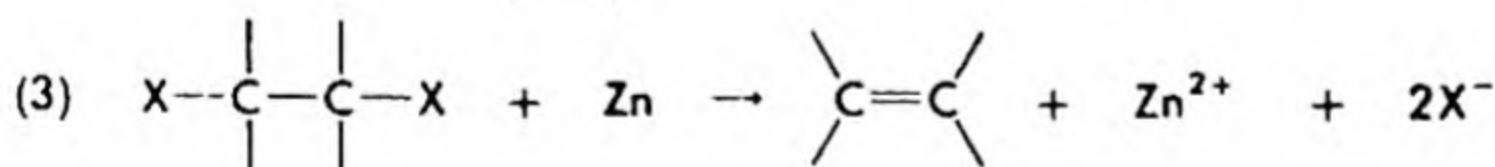
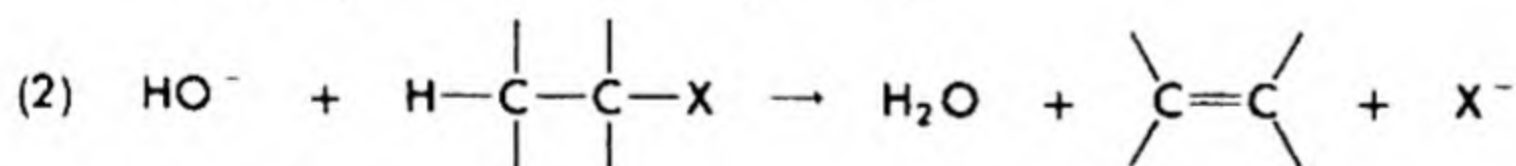
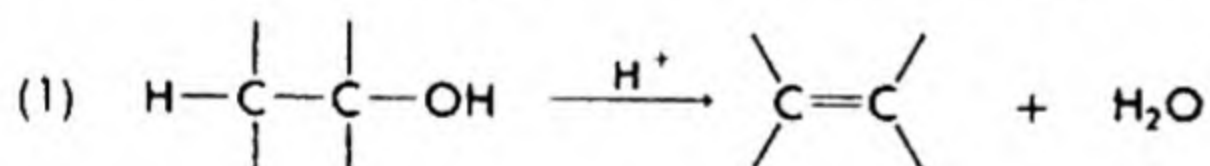
13

Elimination Reactions

13-1 BETA ELIMINATIONS

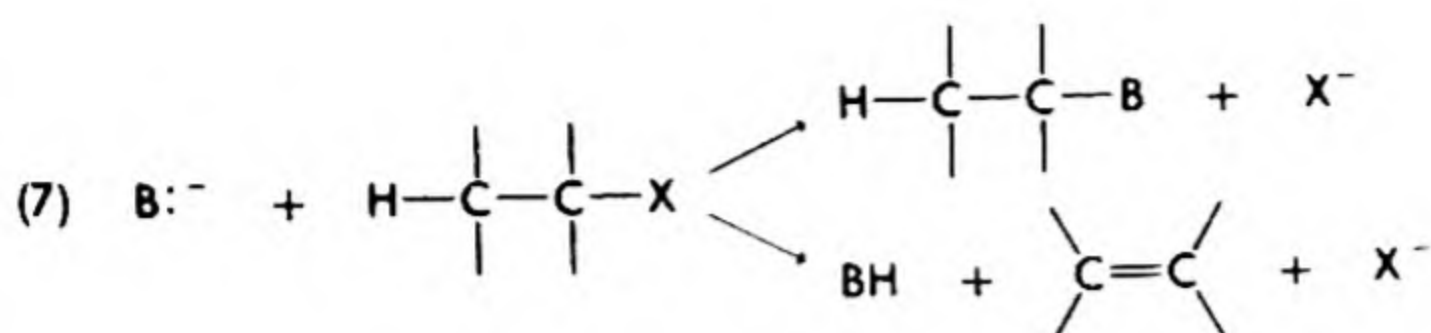
A. General Reaction Types Involved in Eliminations

The formation of double and triple bonds between atoms by the loss of two atoms or groups from vicinal atoms represents the most general type of elimination reactions. These are termed *β-elimination reactions*. Common reactions include formation of olefins by dehydration of alcohols (eq. 1), dehydrohalogenation of alkyl halides (eq. 2), dehalogenation of vicinal dihalides with metals (eq. 3), debromination of vicinal dibromides with potassium iodide (eq. 4), decomposition of quaternary ammonium hydroxides (Hofmann eliminations) (eq. 5), and pyrolysis of esters (eq. 6), among others. Acetylenes can also be prepared by many of these routes, as can carbon-oxygen and carbon-nitrogen multiple bonds.



B. Dehydrohalogenations of Alkyl Halides. General Mechanisms

When an alkyl halide is treated with a base, both substitution and elimination may occur (outline 7). Nucleophilic displacements have been



discussed in Chapter 12 and are considered here only in a role competitive with elimination reactions. As with displacements on alkyl halides, eliminations may show kinetic orders which depend on both alkyl halide and base concentrations (dubbed E2 eliminations, eq. 8) or may have rates dependent only on alkyl halide, being independent of the nature and

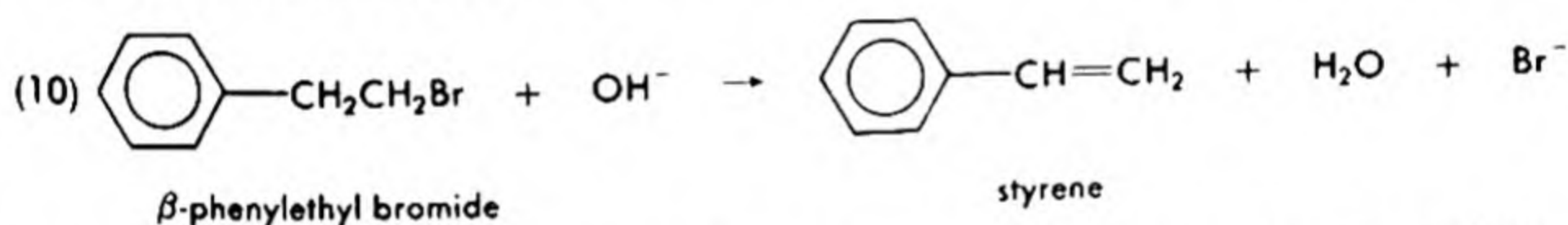
$$(8) \quad \text{rate} = k_2(\text{RX})(\text{B})$$

concentration of base (E1 eliminations, eq. 9). Like $\text{S}_{\text{N}}1$ displacements, the latter elimination process involves carbonium ion intermediates.

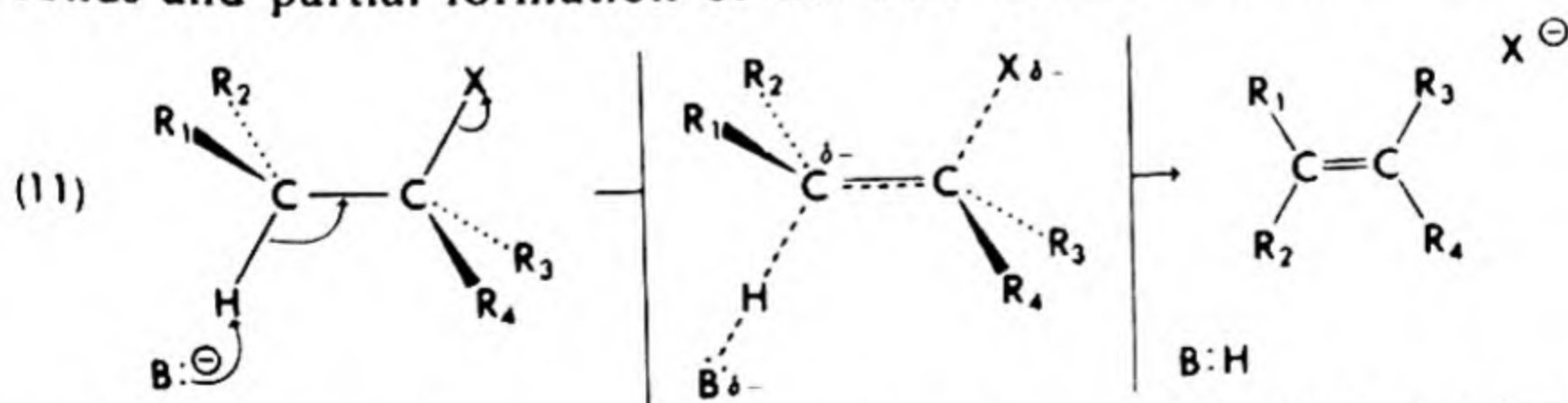
$$(9) \quad \text{rate} = k_1(\text{RX})$$

C. Base-Promoted Elimination Reactions. The Concerted Process

When β -phenylethyl bromide is treated with ethanolic sodium hydroxide at reflux, it is rapidly converted to styrene (eq. 10) in a reaction that

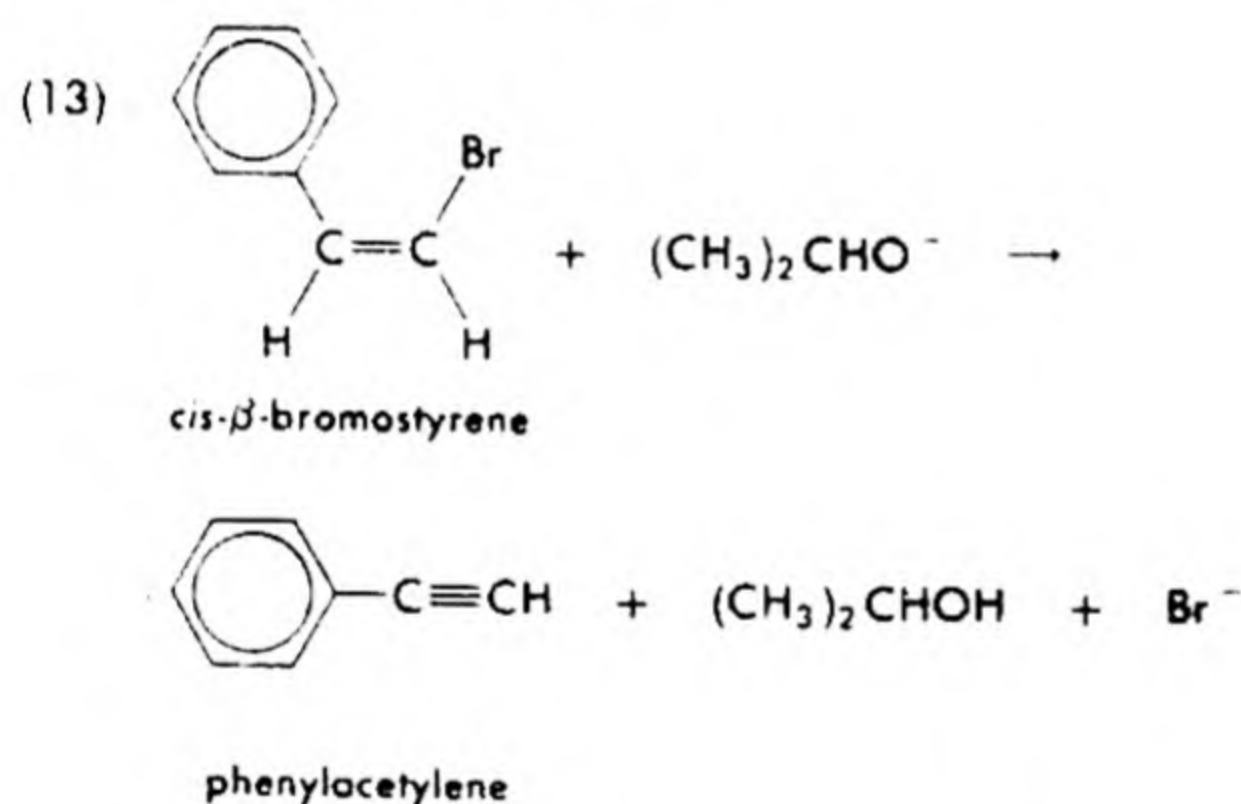
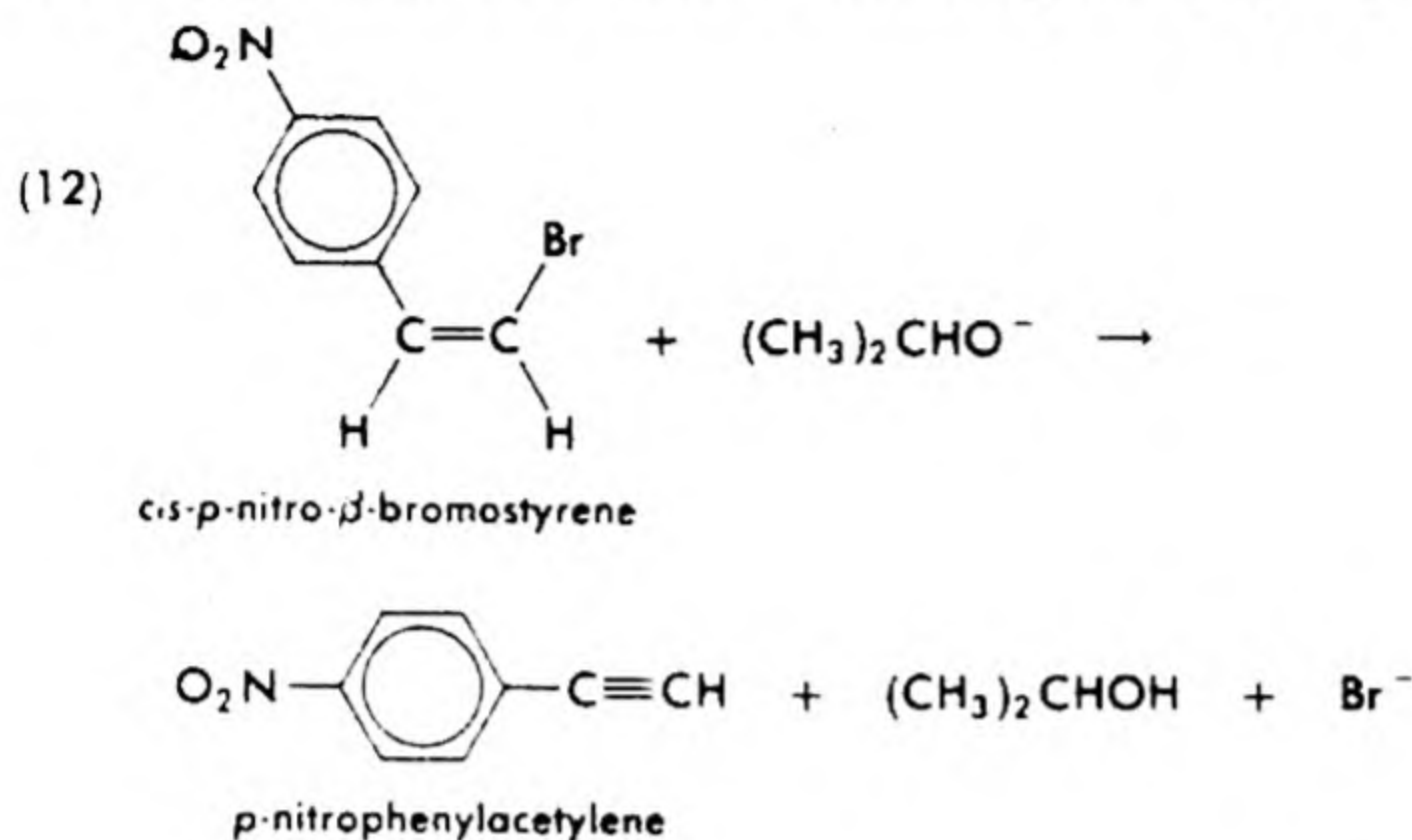


shows first-order dependence on alkyl bromide and first-order dependence on hydroxide ion. A reaction scheme such as eq. (11) may be postulated, in which the base performs a nucleophilic displacement on hydrogen to liberate the electron pair of the hydrogen-carbon bond, which at the same time displaces halide ion from the next carbon atom. The transition state thus involves partial cleavage of the hydrogen-carbon and carbon-halogen bonds and partial formation of the carbon-carbon double bond. This

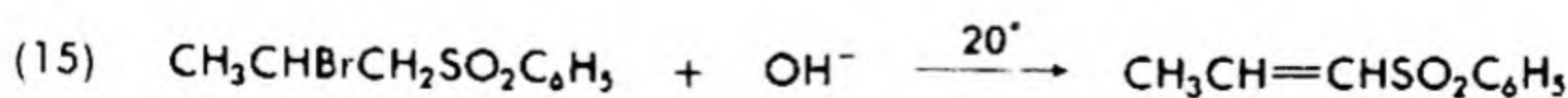
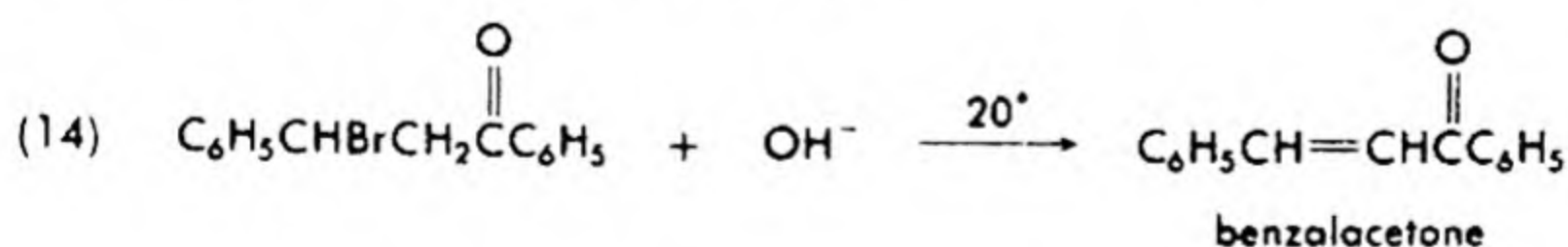


mechanism predicts that the reactivity will increase with (a) increasing strength of the base B, as base strength measures nucleophilicity on hydrogen, (b) increased acidity of the hydrogen—that is, increased ability of the β -carbon to stabilize a negative charge, and (c) stability of X^- as a leaving group. Thus, hydroxide ion is a better elimination reagent than acetate

ion; the latter tends to favor displacement rather than elimination. Even more effective than hydroxide ion is the more basic *t*-butoxide ion. As electron-attracting groups stabilize negative charges, *p*-nitro- β -bromostyrene reacts with sodium isopropoxide in isopropyl alcohol (eq. 12) 1200 times faster than does β -bromostyrene (eq. 13).

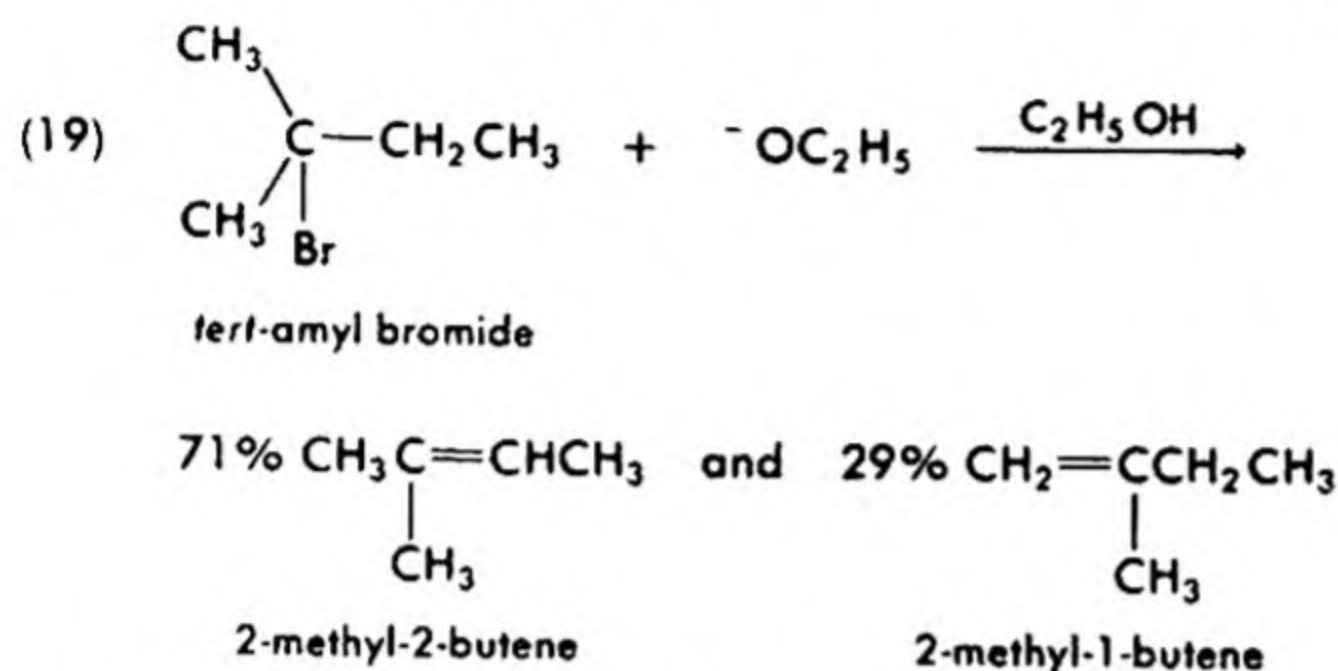
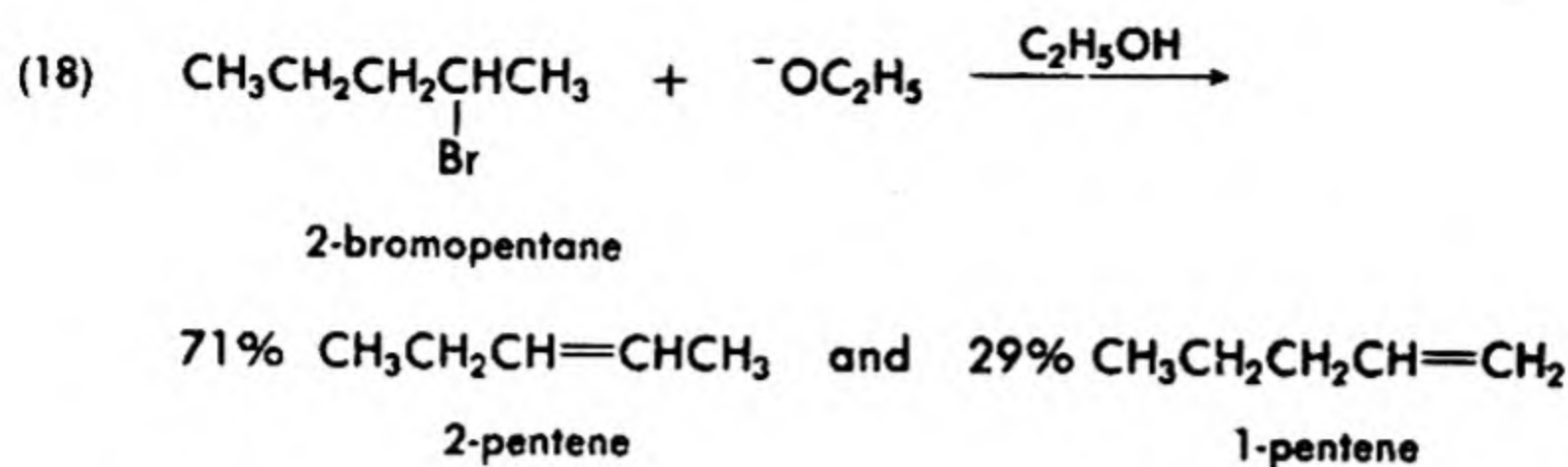


Carbonyl and sulfonyl groups stabilize anions well; therefore, β -halo-ketones, esters, aldehydes, and sulfones are very sensitive to alkali. Examples are given in eqs. (14) and (15).



Just as with displacement reactions in similar solvents, iodides are most reactive, bromides intermediate, and chlorides least reactive.

The proposed mechanism (eq. 11) shows elimination of *trans*-groups, which is usually observed to be preferred over the corresponding *cis*-



(1) *Reagents for Eliminations.* Base strength is remarkably important in affecting rates of elimination reactions. While sodium or potassium hydroxide are the strongest bases available in aqueous solution, sodium ethoxide in ethanol is stronger. Potassium *tert*-butoxide is utilized for eliminations, as it is very bulky and consequently sterically hindered for displacement reactions where it must be brought close to a polysubstituted carbon atom rather than to a monovalent hydrogen atom as in elimination. It is a reactive base when dissolved in *tert*-butyl alcohol, but its reactivity is increased tremendously when dissolved in the highly polar solvent, dimethyl sulfoxide, CH_3SOCH_3 . Table 13-2 lists the relative rates for the reaction given in eq. (20) with a 1*M* solution of various bases.

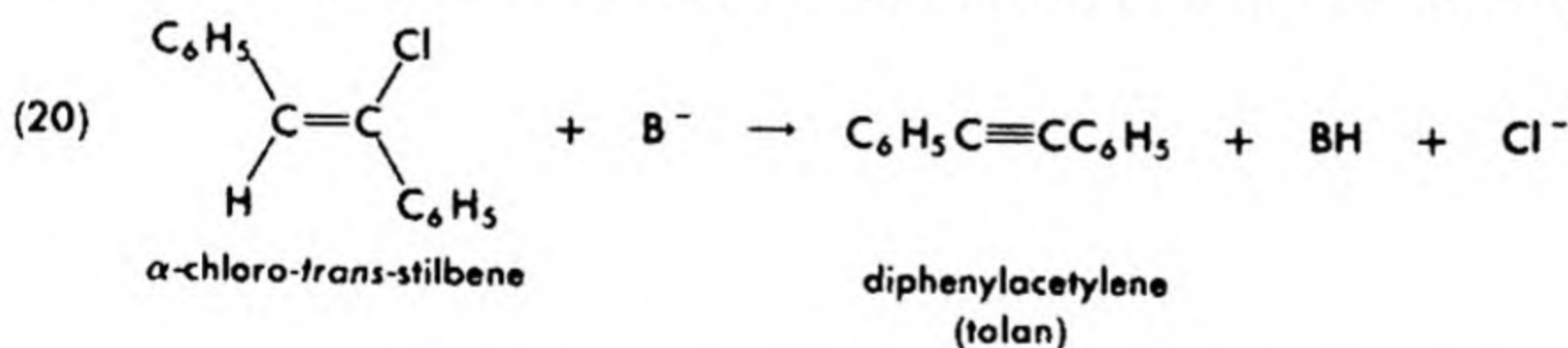


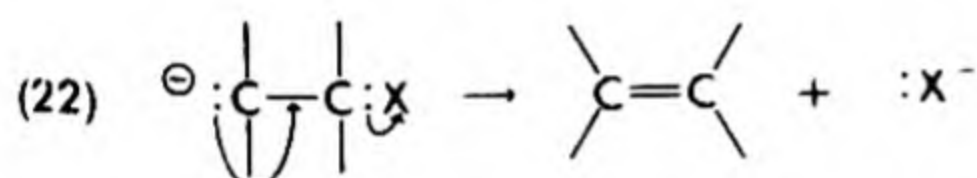
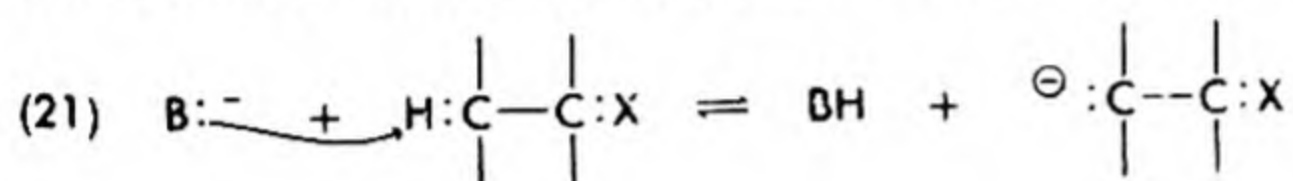
TABLE 13-2. Variation of Rate of Elimination with Base Used

Base	Temp., °C	Half-life, sec.	Relative Rate at 20°
NaOH in C ₂ H ₅ OH	97	765	1
KOC(CH ₃) ₃ in (CH ₃) ₃ COH	25	3.9×10^4	230
KOC(CH ₃) ₃ in CH ₃ SOCH ₃	20	5.9×10^{-3}	3×10^9

- Amines may also be used as bases in elimination reactions. Hindered tertiary amines are generally used to avoid formation of quaternary ammonium halides by displacement.

Since elimination processes generally have higher activation energies than displacements, eliminations are conducted at high temperatures when possible—for example, by boiling in quinoline or by dropping the alkyl halide onto molten potassium hydroxide.

(2) *Base-promoted Elimination Reactions. The Carbanion Intermediate Process.* The bimolecular process discussed thus far is a concerted one (eq. 11) in which the transition state involves all of the bonds concerned in the transformation of base and alkyl halide to the conjugate acid of the base, olefin, and halide ion, although not all of them necessarily to the same extent. Another mechanism, which has the same kinetic order (eq. 8) as the concerted process, is given in eqs. (21) and (22). This process has an intermediate *carbanion*, that is, a carbon atom bearing a free elec-

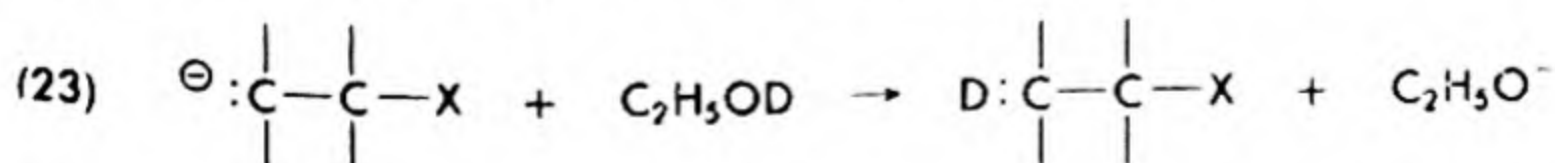


tron pair (Fig. 13-1) and a negative charge. This intermediate may react with BH to return to starting material (or to an isomer of the starting material) (reverse of eq. 21) or may lose halide ion (eq. 22). When the

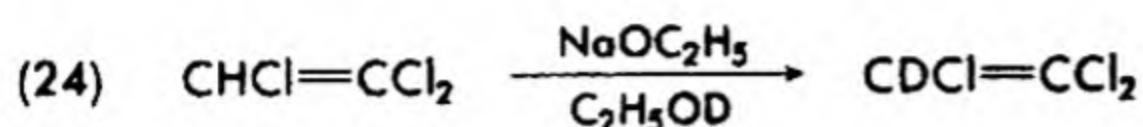


Fig. 13-1. MO Cloud and MO Diagram for a Carbanion.

loss of halide ion is much faster than reaction with BH, it has not been possible to distinguish this process with certainty from the concerted process, although subtle arguments have been raised in its behalf. On the other hand, when the reverse of eq. (21) is faster than or at least competitive with loss of halide ion, the mechanism can be demonstrated by conducting the reaction in deuterated solvent. If the base is $\text{C}_2\text{H}_5\text{O}^-$ and the solvent used $\text{C}_2\text{H}_5\text{OD}$, reaction of the carbanion gives deuterated starting material (eq. 23), which can be isolated after the reaction is carried



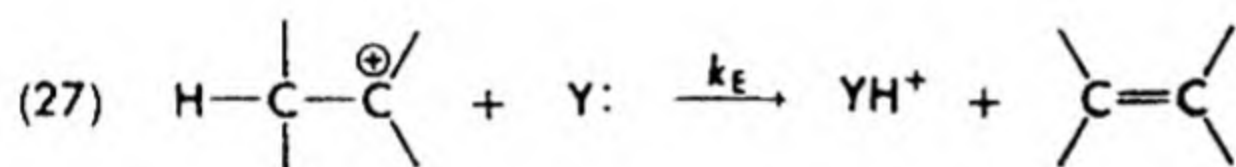
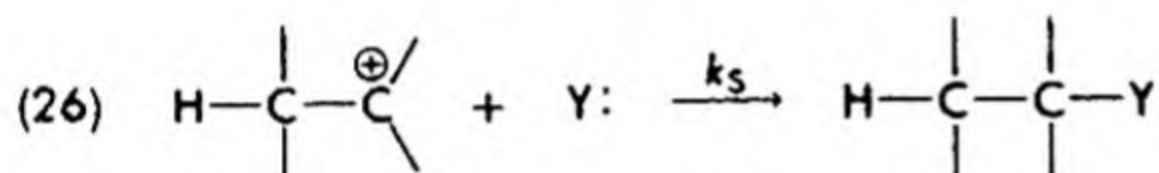
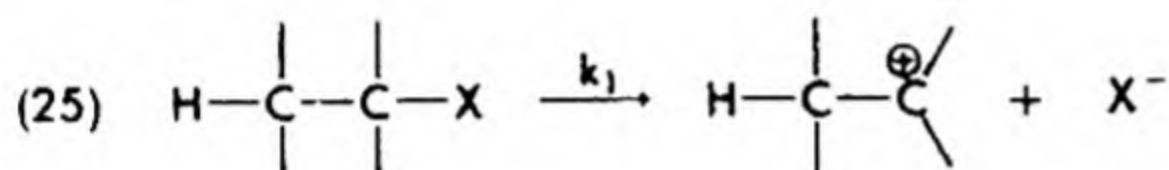
part way. This has been done in a number of cases, one example of which is given in outline (24).



The carbanion process is favored in eliminations to highly halogenated acetylenes, whenever highly stabilized carbanions are involved (α to carbonyl or sulfonyl groups) and when the *trans* concerted process is inoperable (*cis* eliminations, eliminations from nondiaxial conformations in cyclohexanes, etc.).

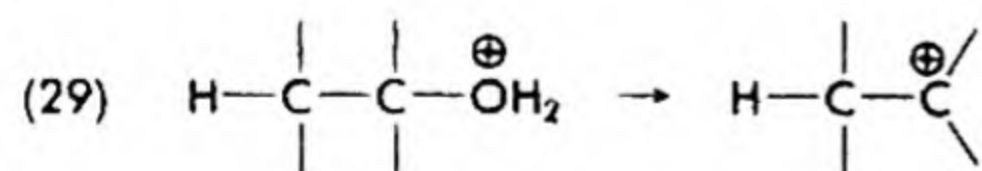
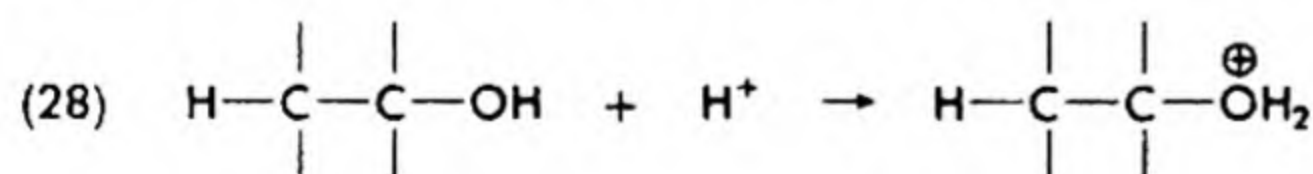
D. Dehydrohalogenations Involving Carbonium Ion Intermediates

As discussed in the chapter on nucleophilic displacements, carbonium ions undergo not only coordination with nucleophiles to give net displacement, but also proton transfer to base to give olefins (eqs. 25 through 27).

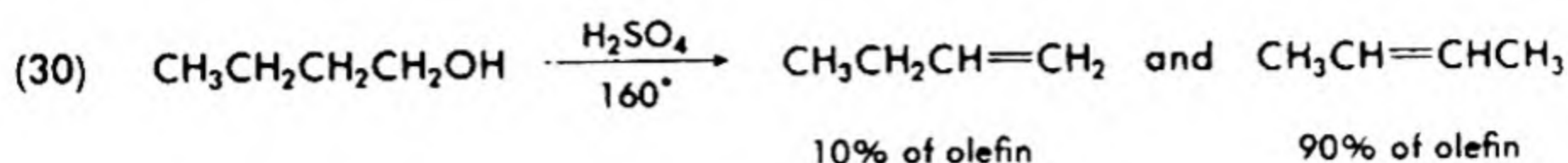


Both of these processes have eq. (25) as the slow step, with the proportion of olefin in the final product determined by the ratio $k_E/(k_s + k_E)$. The reactions are zero order in base (eq. 9), as the slow step does not have base in its transition state.

(1) *Dehydrations of Alcohols.* A strong proton donor or Lewis acid is needed for dehydration of alcohols to olefins. Acid is required to form an oxonium ion (eq. 28), which then loses water to give a carbonium ion (eq. 29), which then may lose a proton to give olefin (eq. 27). The carbonium ion mechanism is indicated by the relative ease of dehydration of

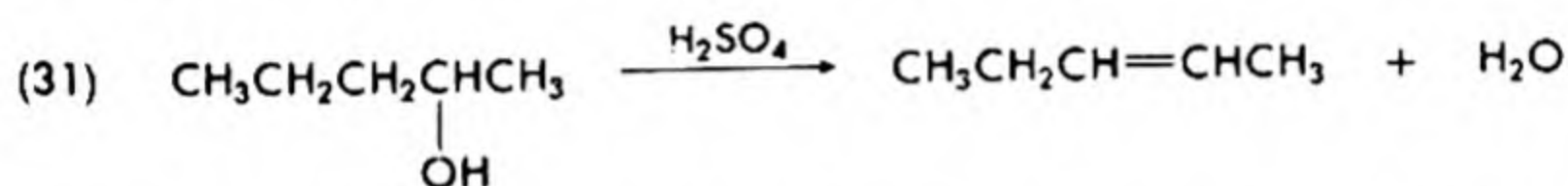


tertiary alcohols and much greater difficulty of dehydration of primary alcohols than secondary. As with all carbonium ion reactions, rearrangements occur readily. Thus 1-butanol gives a mixture of 1- and 2-butenes (outline 30).

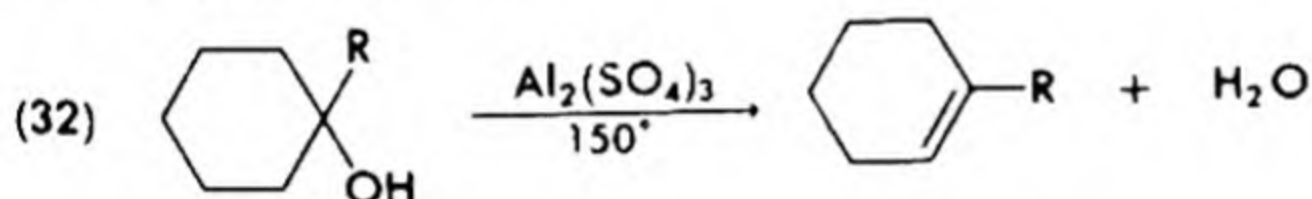


Nonvolatile acidic materials suitable for dehydrations are sulfuric acid, potassium bisulfate, sulfonic acids, phosphoric acid, polyphosphoric acid, and phosphorus pentoxide. Alumina is also effective at higher temperatures. Tertiary alcohols and other very reactive alcohols can often be dehydrated even with iodine catalysis, wherein iodine manifests weak Lewis acid character.

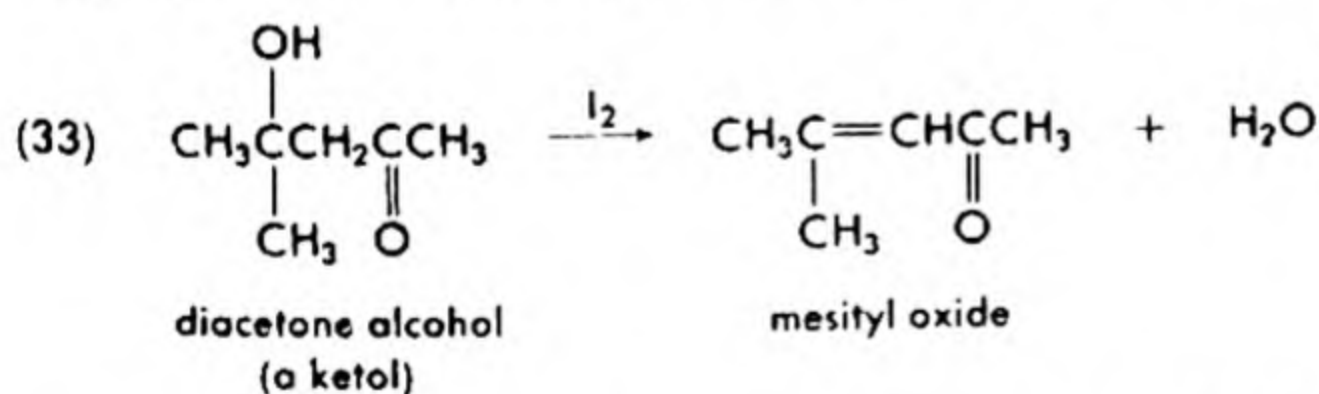
Industrially, alcohols are prepared by hydration of lower olefins available from cracking of petroleum fractions. Consequently, dehydrations have no practical value among lower alcohols, except as laboratory procedures. Yields of olefins are often good. The Saytzeff rule is obeyed. For example, from the dehydration of 2-pentanol (eq. 31), a yield of 80% of 2-pentene is possible, indicating that at least 80% of the dehydration product is this compound. Similarly, 80% yields of 1-methylcyclohexene



and other 1-alkylcyclohexenes are reported from the corresponding 1-alkylcyclohexanols.



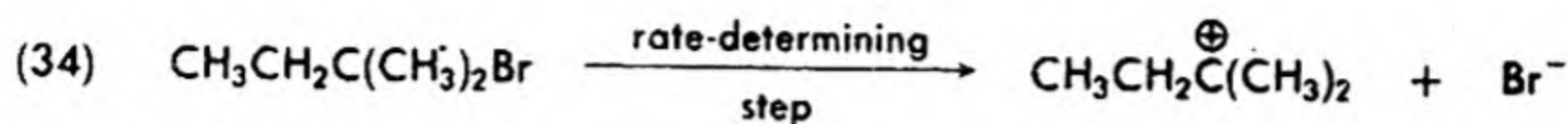
An example of dehydration of a *ketol* with iodine (Hibbert method) is the preparation of mesityl oxide in 91% yield from diacetone alcohol.



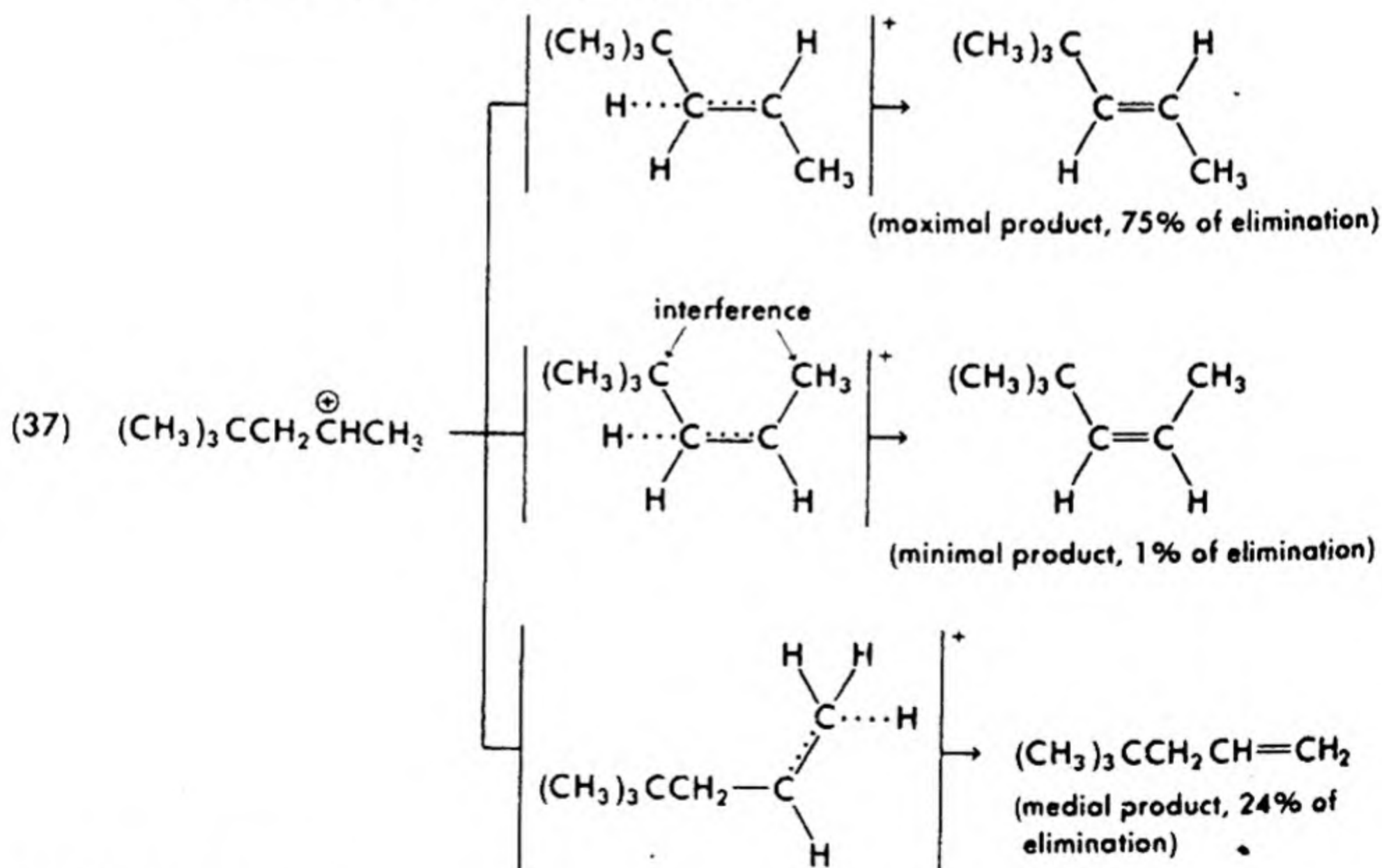
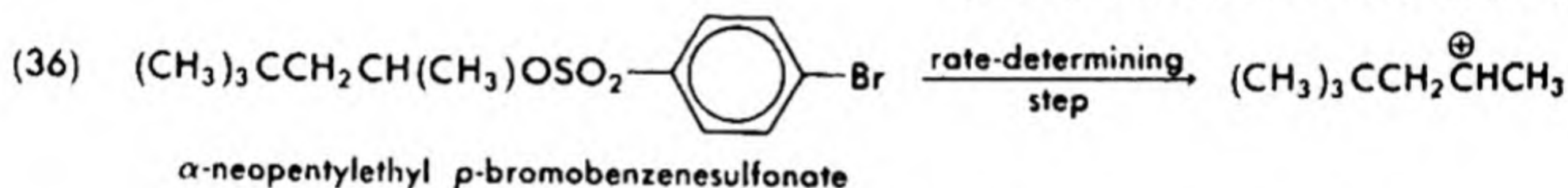
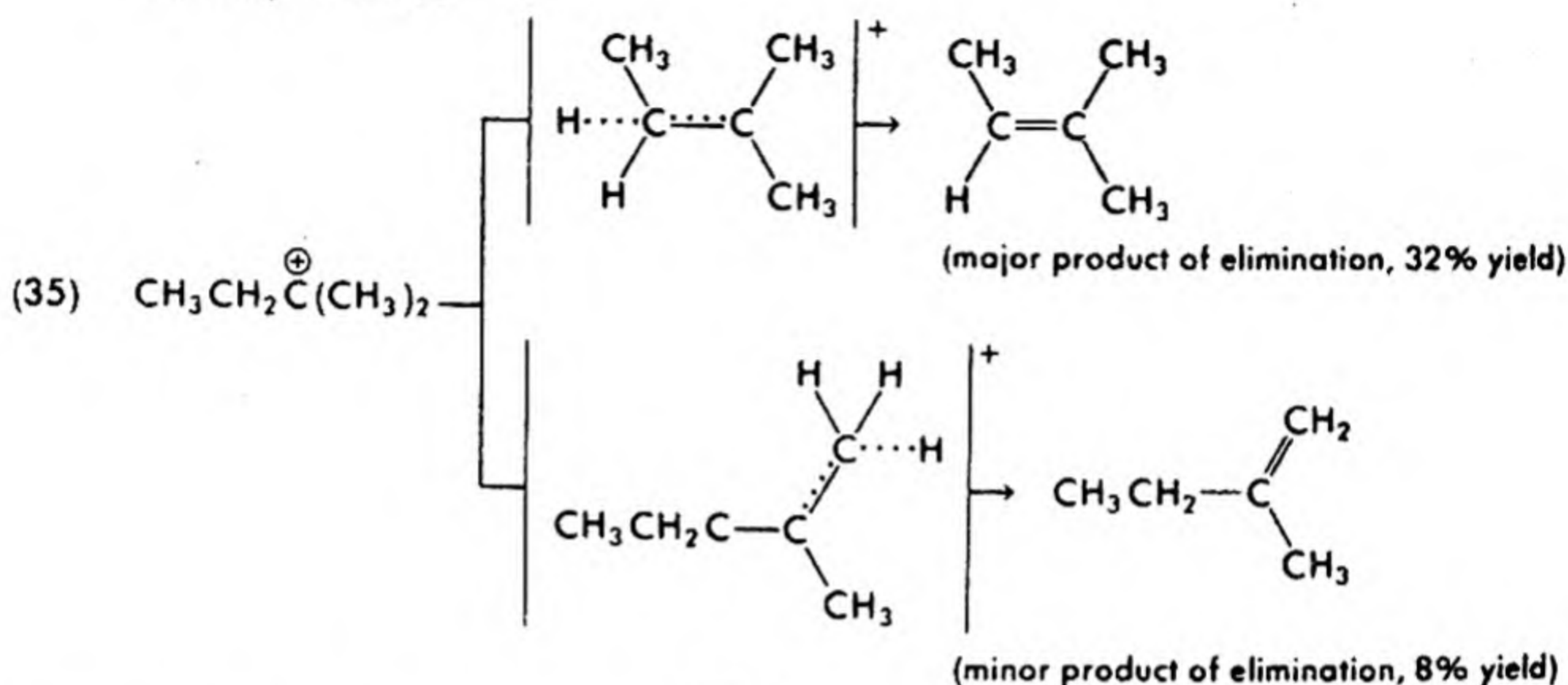
(2) *Other Carbonium Ion Eliminations.* Olefin formation from tertiary and some secondary alkyl halides and from many alkyl sulfonates and alkyl sulfates can occur by a carbonium ion mechanism. Pyrolysis of sulfonates may follow a different course (§13-2B).

Characteristically, such carbonium ion eliminations are nonstereospecific; *cis*-eliminations occur as easily as *trans*-eliminations. Also, characteristically, the stability of the intermediate carbonium ion influences the reaction rate. Finally, the transition state between the carbonium ion

and olefin must have enough similarity to the latter, in that olefin stability has considerable effect on the course of the reaction (but not its rate, since the first TS is rate-determining).



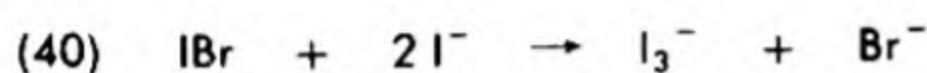
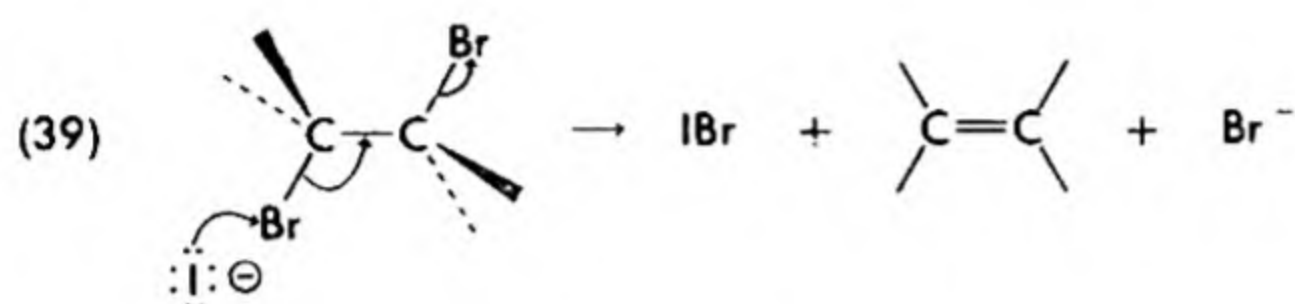
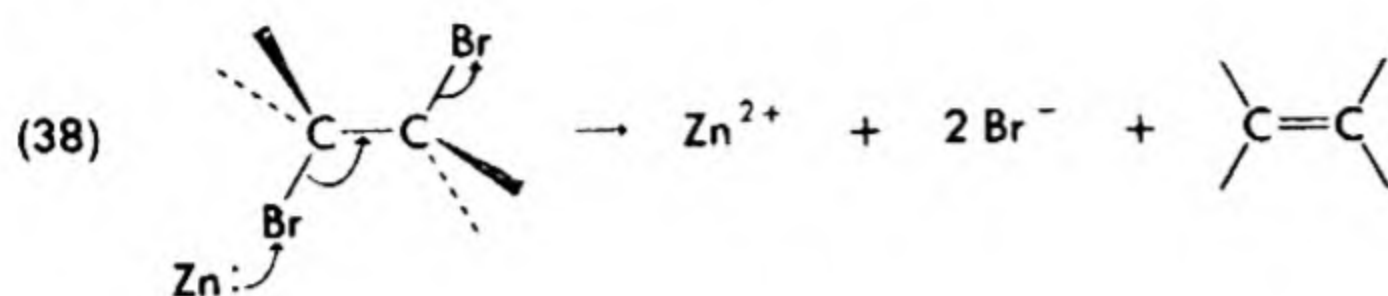
tert-amyl bromide



E. Dehalogenations

Treatment of dihalides with metals such as zinc leads to olefin formation, with *trans* elimination of groups observed when possible (eq. 38).

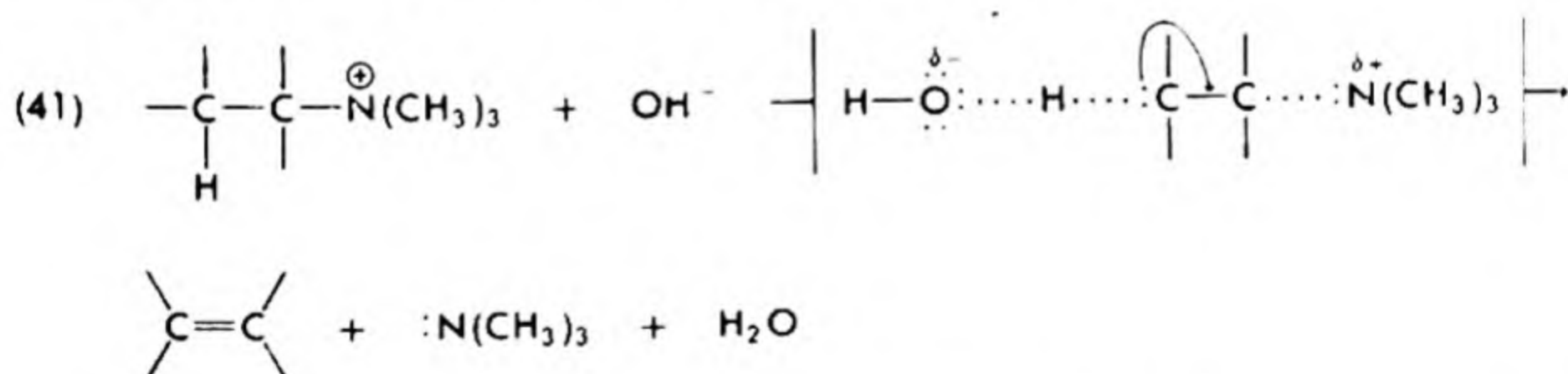
A similar mechanism obtains with iodide ion on dibromides (eqs. 39 and 40).



Such reactions are useful for "protecting" double bonds by addition of bromine. Then a reaction elsewhere in the molecule to which the original double bond might have been sensitive may be conducted and this may be followed by regeneration of the olefinic linkage. Since both bromine addition (§14-2A) and debromination are *trans* processes, the spatial arrangement of the original olefin is conveniently restored in the final olefin.

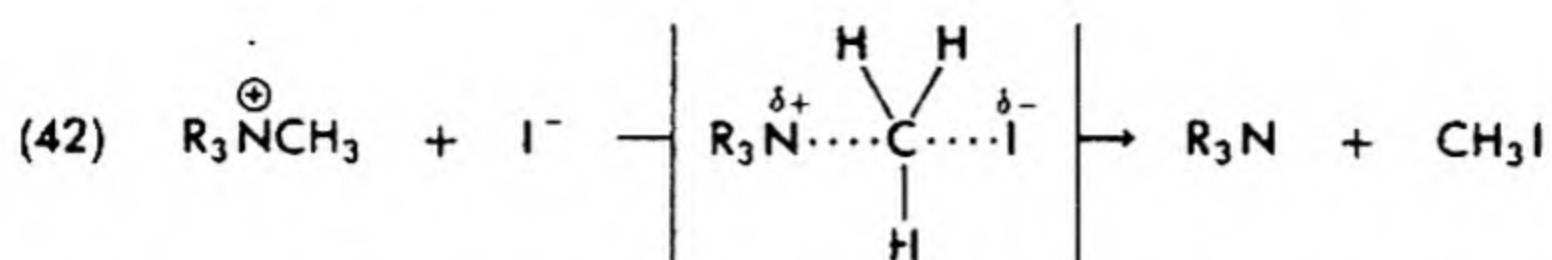
F. Hofmann Elimination Reactions

Elimination of quaternary nitrogen from a quaternary ammonium hydroxide is quite similar to dehydrohalogenation. The positive nitrogen atom is strongly electron-attracting. The hydroxide ion of the compound itself acts to remove the activated hydrogen atom (eq. 41).



Since the quaternary ammonium hydroxide furnishes its own basic attacking ion, as well as its own electron-attracting leaving group, no external reagent or catalyst is required.

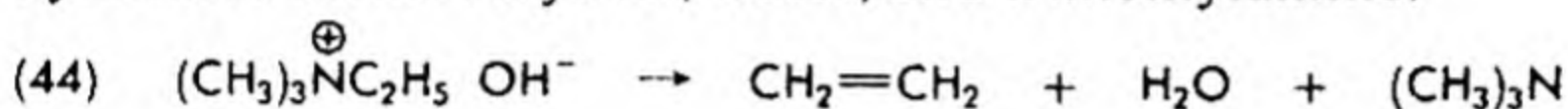
Heating a quaternary ammonium halide decomposes the salt in such a way that the primary alkyl halide of the smallest alkyl radical is formed. If the quaternary ammonium halide contains a methyl group, the methyl radical is the one lost, which is consistent with the order of reactivity in direct displacement reactions (eq. 42).



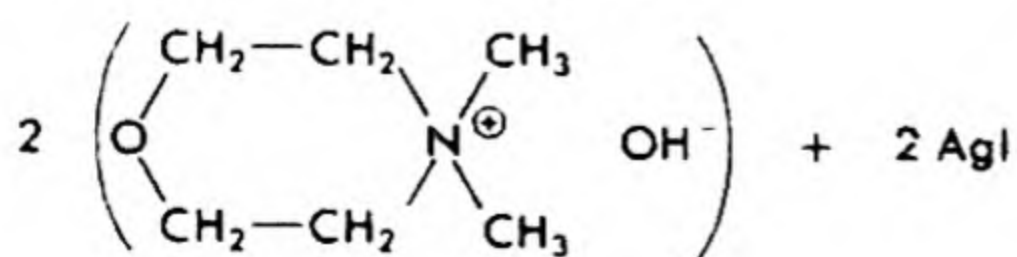
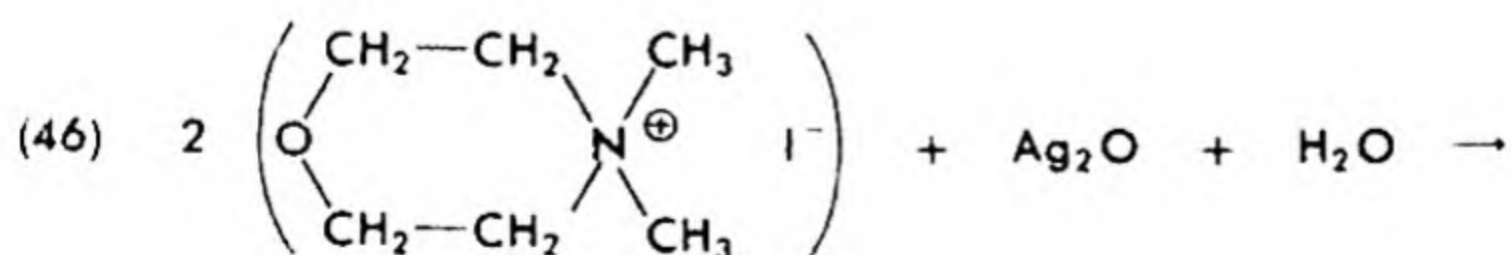
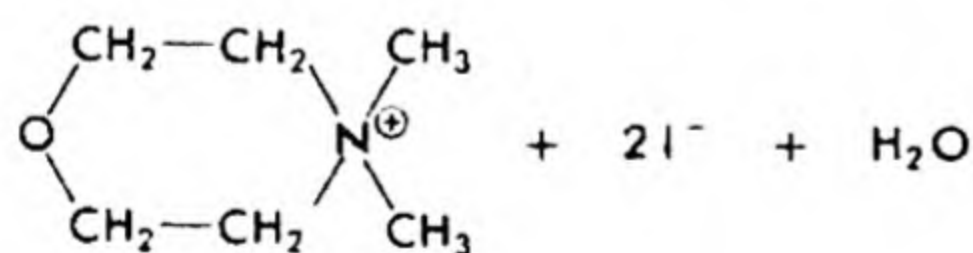
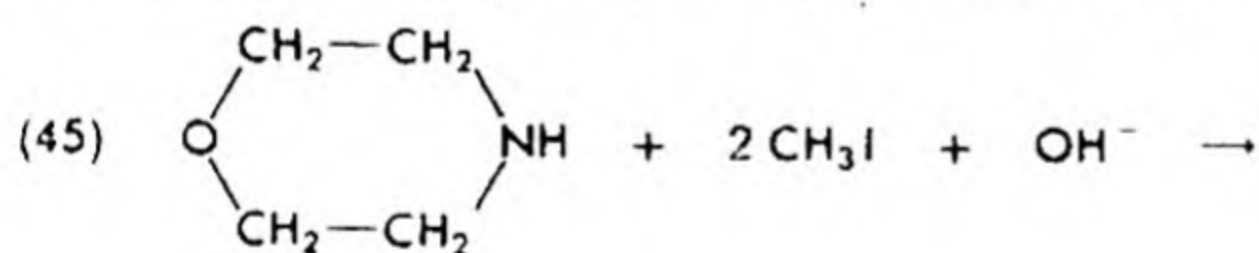
However, if the quaternary ammonium halide is treated with moist silver oxide to form the quaternary ammonium hydroxide and this is decomposed, the reaction takes a different course. In this case, whenever possible, elimination is the preferred reaction. A methyl group is removed only if there are no β -hydrogens, as, for example, in tetramethylammonium hydroxide. In that case, direct displacement occurs to give methanol. Higher groups form double bonds. Thus, trimethylethylammonium

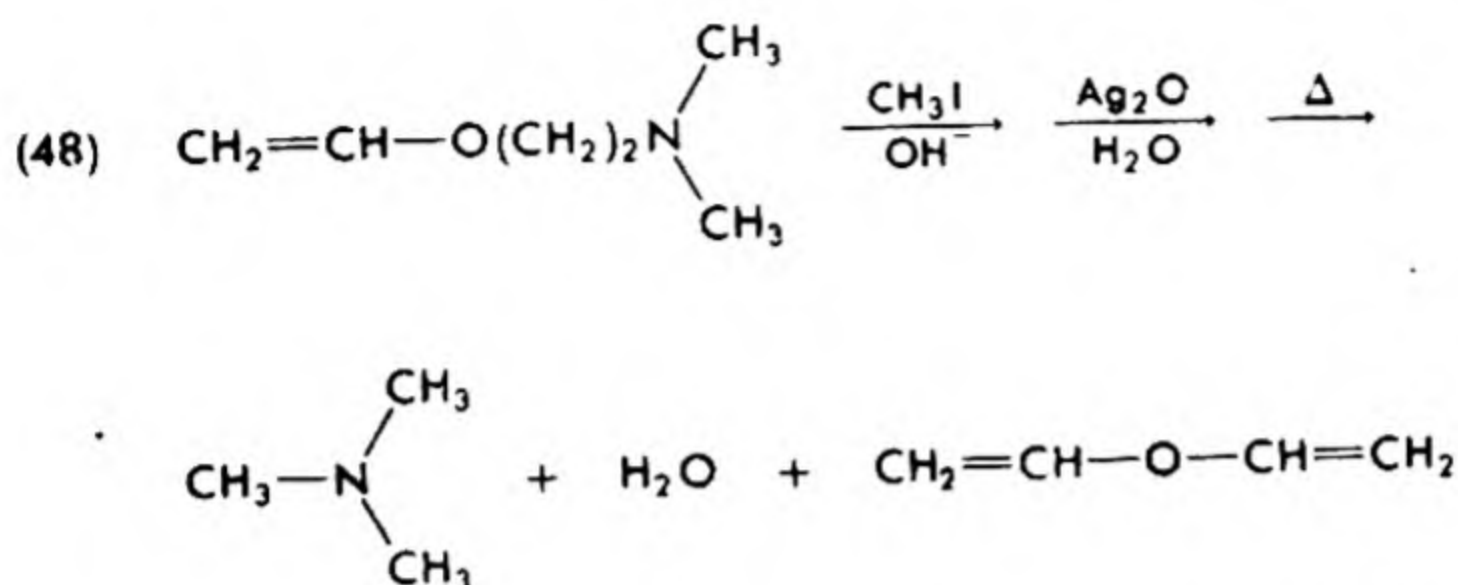
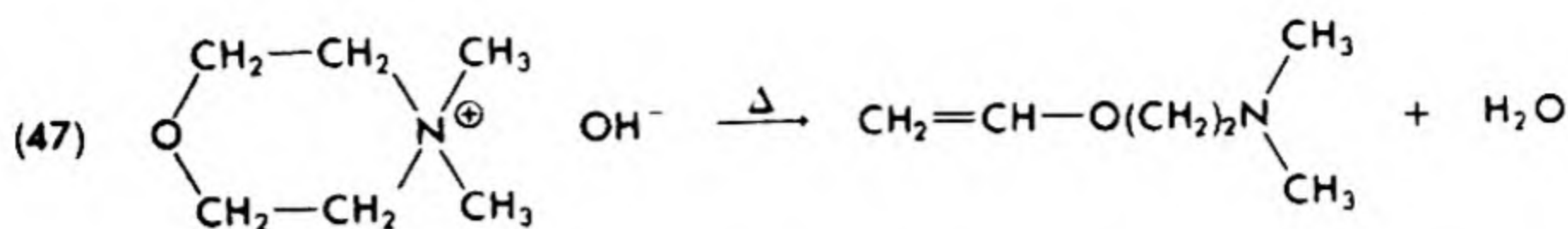


hydroxide forms ethylene, water, and trimethylamine.

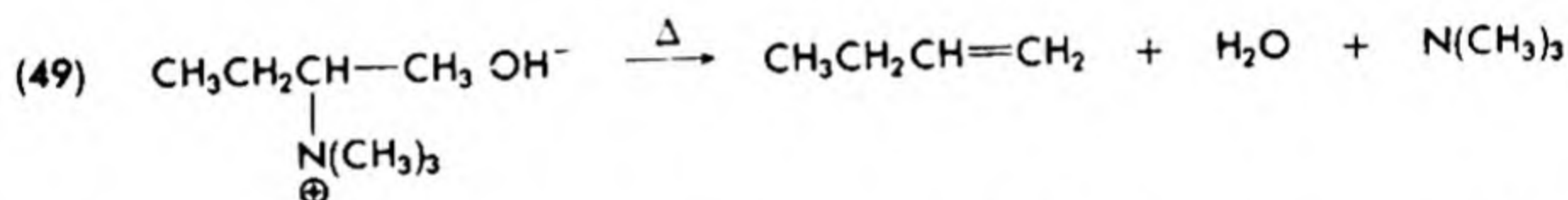


Hofmann elimination reactions are very useful in the determination of structures of naturally occurring amino compounds. An amine is methylated to give a quaternary ammonium salt, which is converted to the base with silver oxide. This is then decomposed. Heating the salt with potassium hydroxide is also effective. If more than one large group is present on the nitrogen atom, they can be removed one after another by repetition of the methylation, base formation, and deamination. The process is called the Hofmann exhaustive methylation and degradation of amines, since it was first used by August W. Hofmann in his structural analysis of amines. Application of the method to morpholine gives the results shown in eq. (45) through outline (48).

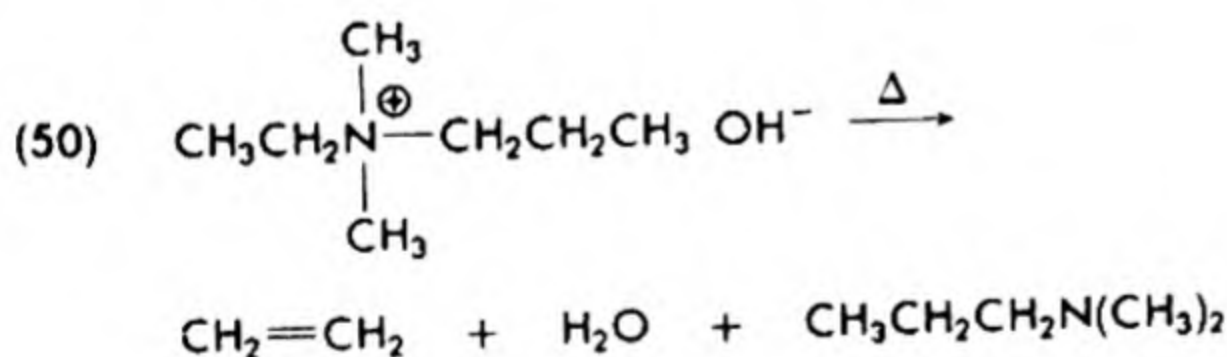




Hofmann eliminations do not follow the Saytzeff rule (§13-1C). The tendency in Hofmann elimination of alkyl groups is to give the *least* substituted olefin. Thus, *sec*-butyltrimethylammonium hydroxide gives largely 1-butene (eq. 49). The reaction is thus used to prepare terminal

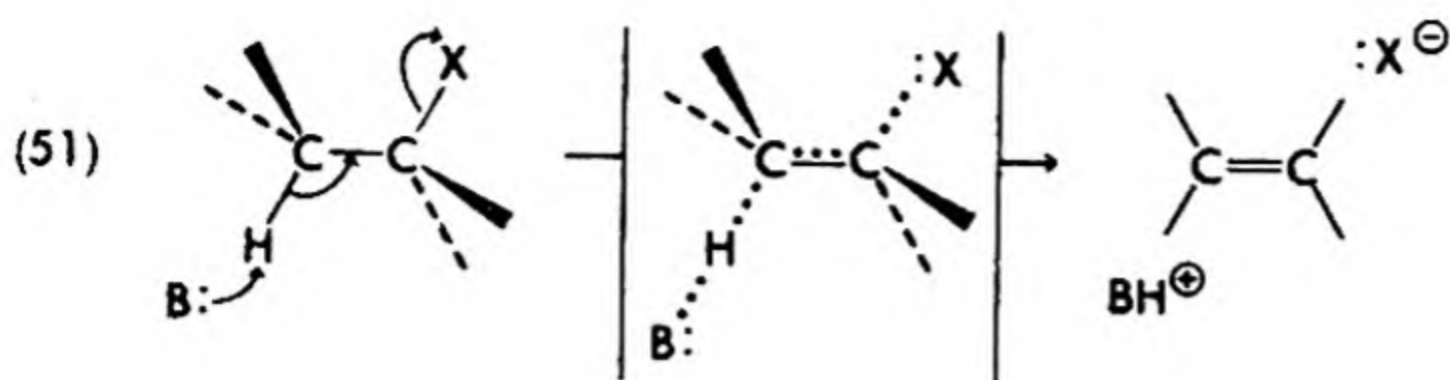


olefins. For similar reasons, ethyl-*n*-propyldimethylammonium hydroxide gives principally ethylene and dimethyl-*n*-propylamine (eq. 50) in preference to propylene and dimethylethylamine.



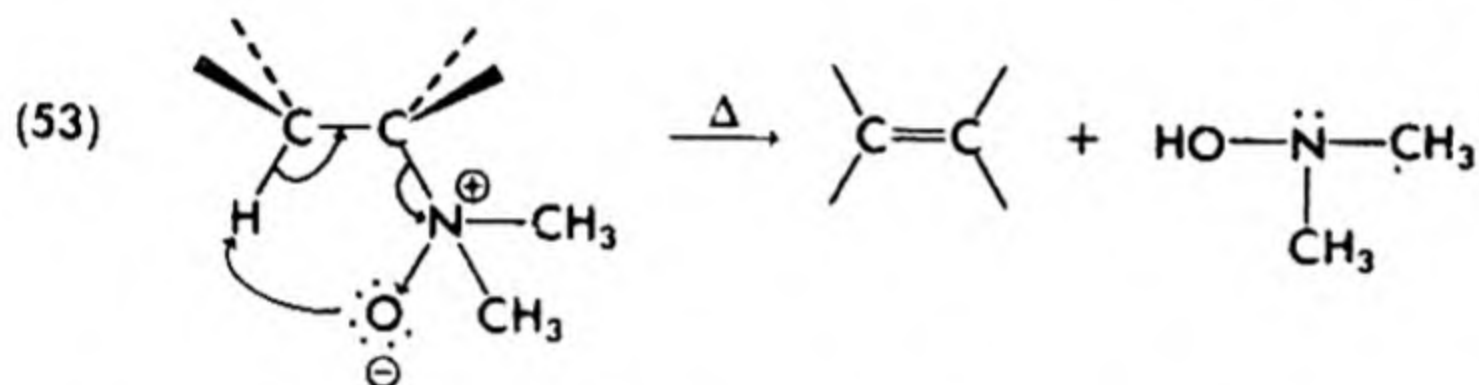
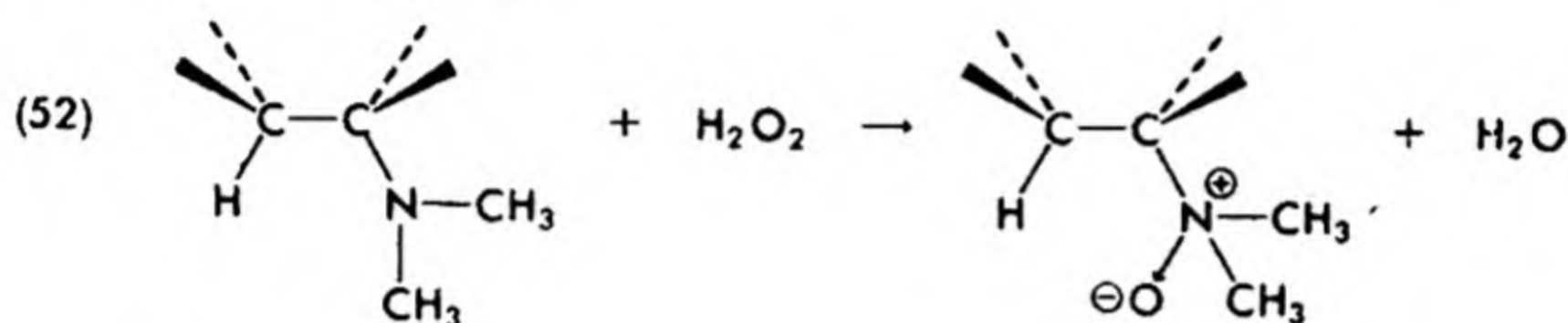
G. Stereochemical Preferences

As mentioned several times already, β -elimination reactions involving attack by base on a substrate to give olefin or acetylene proceed with considerably greater facility when the departing groups are *trans* than when they are *cis*. This is usually rationalized by assuming that the *trans* eliminations are concerted, with transfer of a proton to base, formation of the carbon-carbon double bond, and departure of the leaving group occurring in a synchronous fashion (eq. 51). The *trans*-coplanar requirement for the transition state is analogous to that requiring inversion in the direct displacement process.

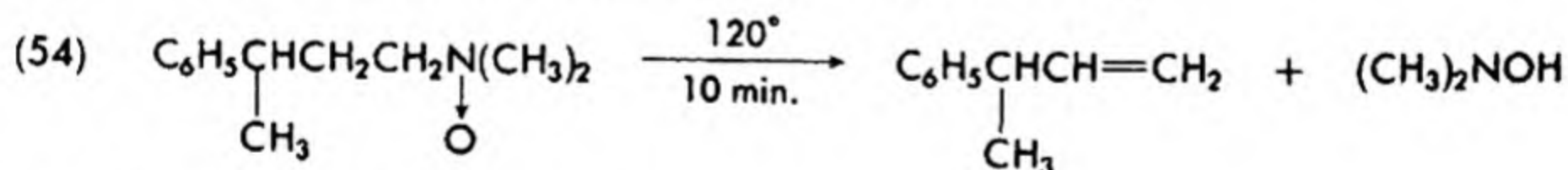
13-2 PYROLYTIC *cis*-ELIMINATIONS

A. Amine-Oxide Decompositions

A new variant of the Hofmann elimination involves the pyrolysis of an amine oxide (eq. 53) prepared by the action of hydrogen peroxide on a tertiary amine (eq. 52).

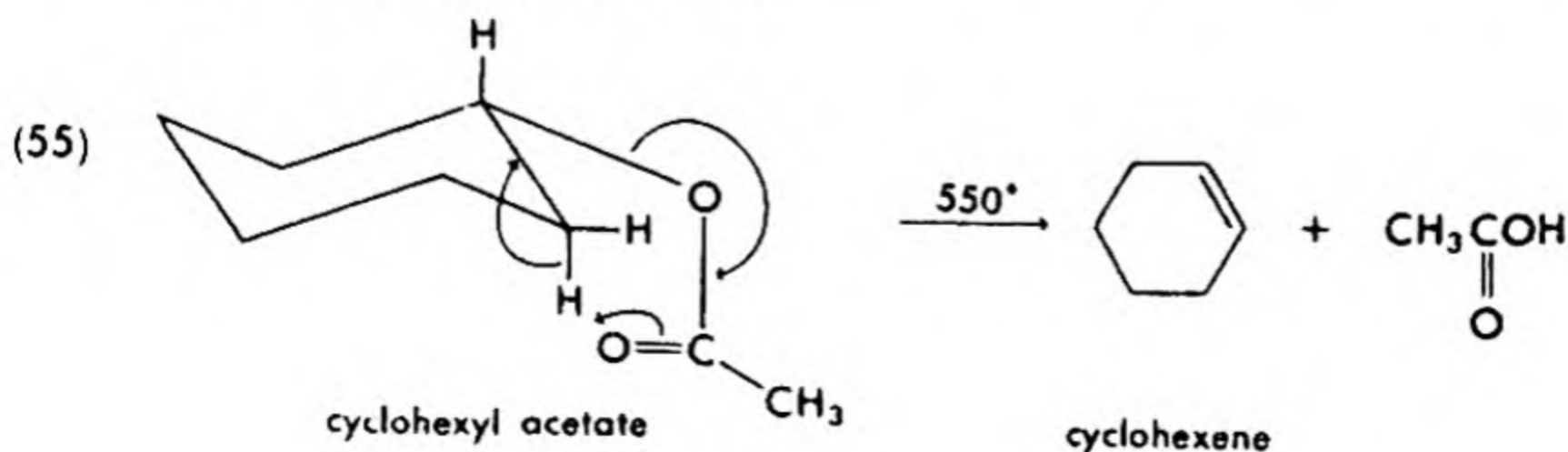


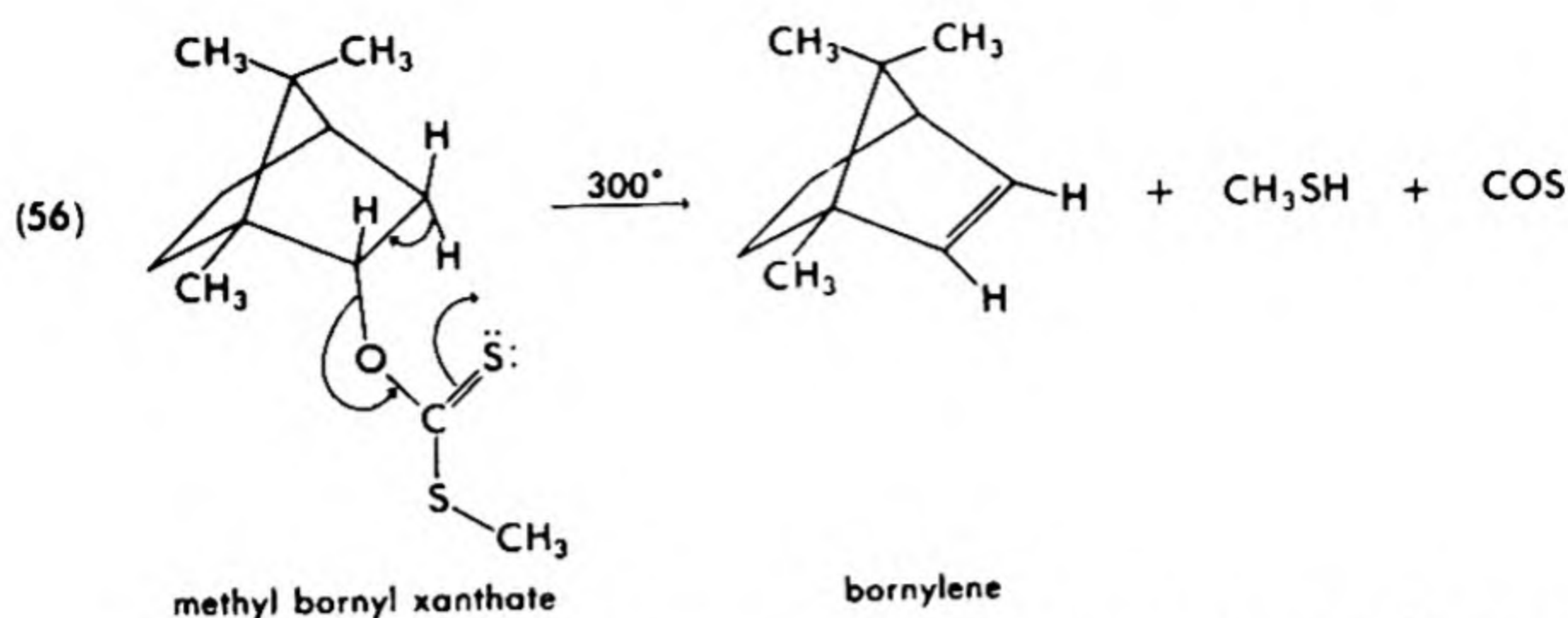
This reaction, which is now called the Cope elimination, occurs at rather mild temperatures. The example in eq. (54) shows a use of the reaction under mild conditions to give an unconjugated olefin, without the isomerization to conjugated olefin anticipated with the use of alkali and higher temperatures (normal Hofmann conditions).



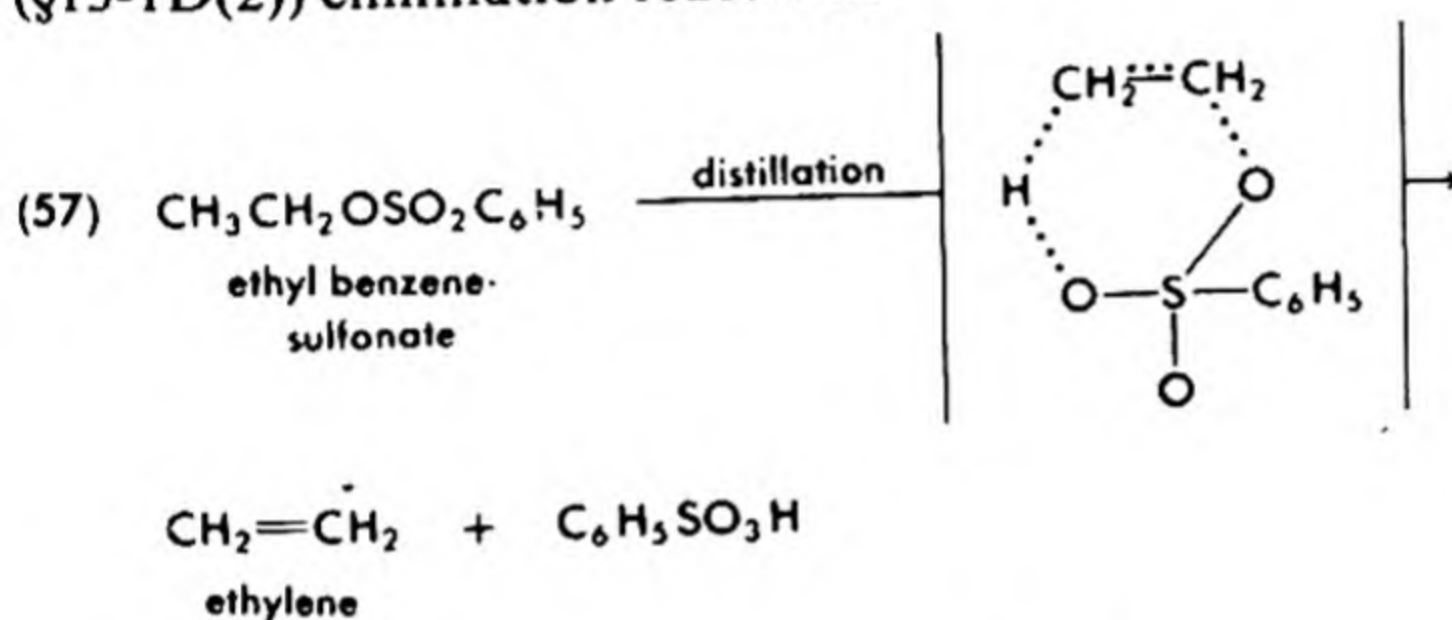
B. Other Pyrolytic Eliminations

The pyrolysis of esters (e.g., acetates, benzoates, xanthates) leads, often in excellent yields, to olefins (eq 55). These, like the amine oxide pyrolysis are *cis* eliminations. They have great utility in synthesis. Preparation of xanthates is given in §18-3D.



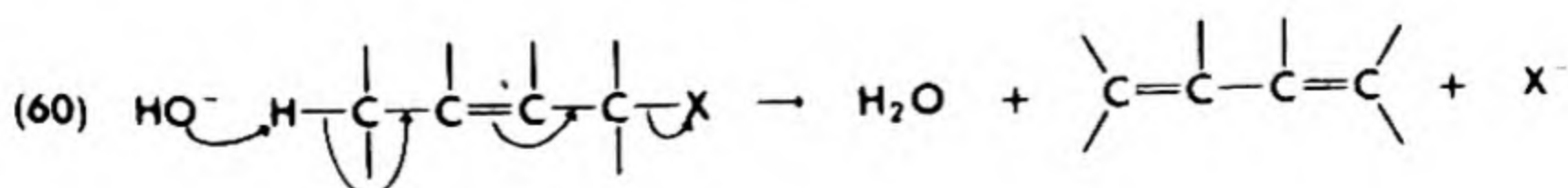
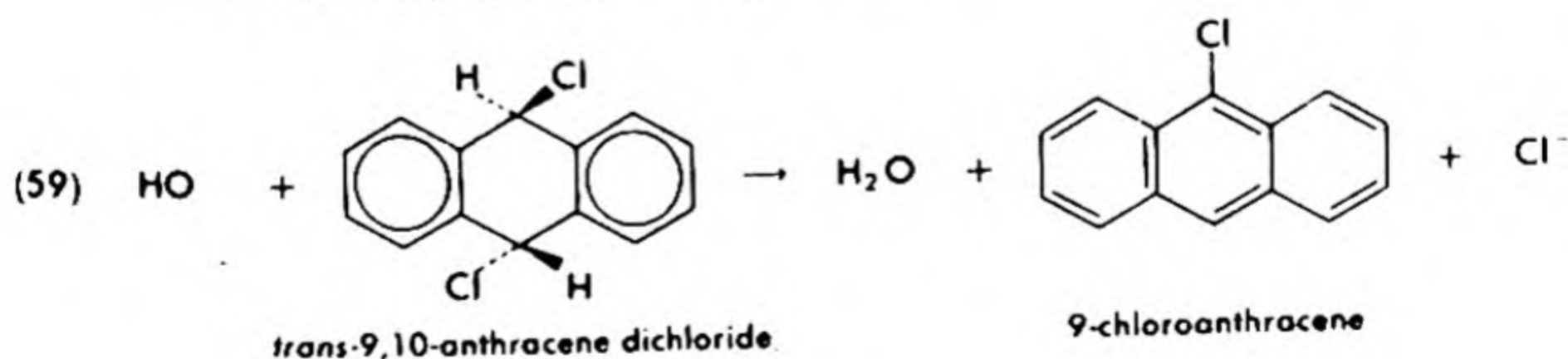
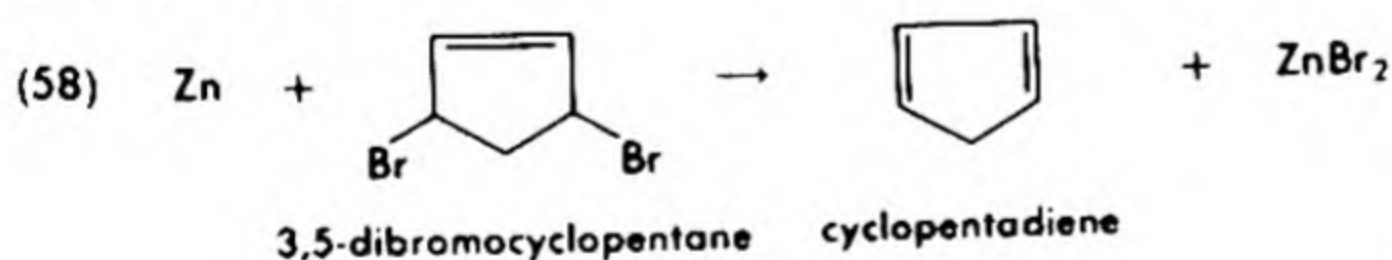


Pyrolysis of alkyl sulfates and sulfonates may also involve a cyclic mechanism (eq 57) although at lower temperatures or in solution these compounds undergo base-catalyzed (§13-1C) and carbonium ion (§13-1D(2)) elimination reactions.



13-3 1,4-CONJUGATE ELIMINATIONS

The removal of groups or atoms from the carbon atoms that flank a double bond to give a diene is termed *1,4-conjugate elimination*. Examples are given in eqs. (58) and (59). The reaction course can be rationalized as in eq. (60).

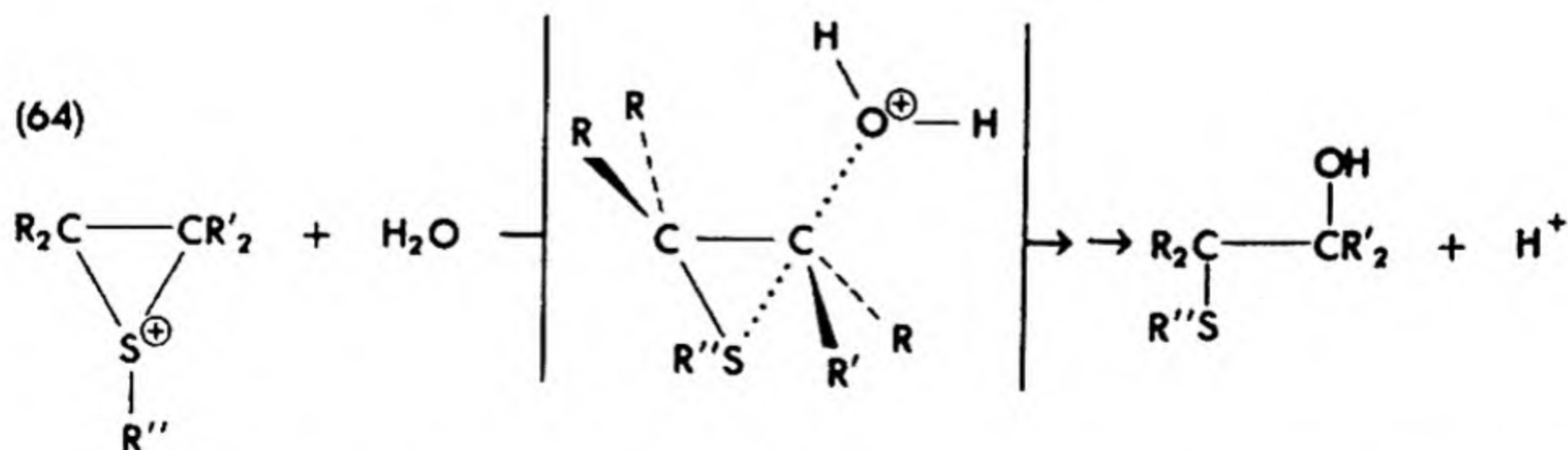
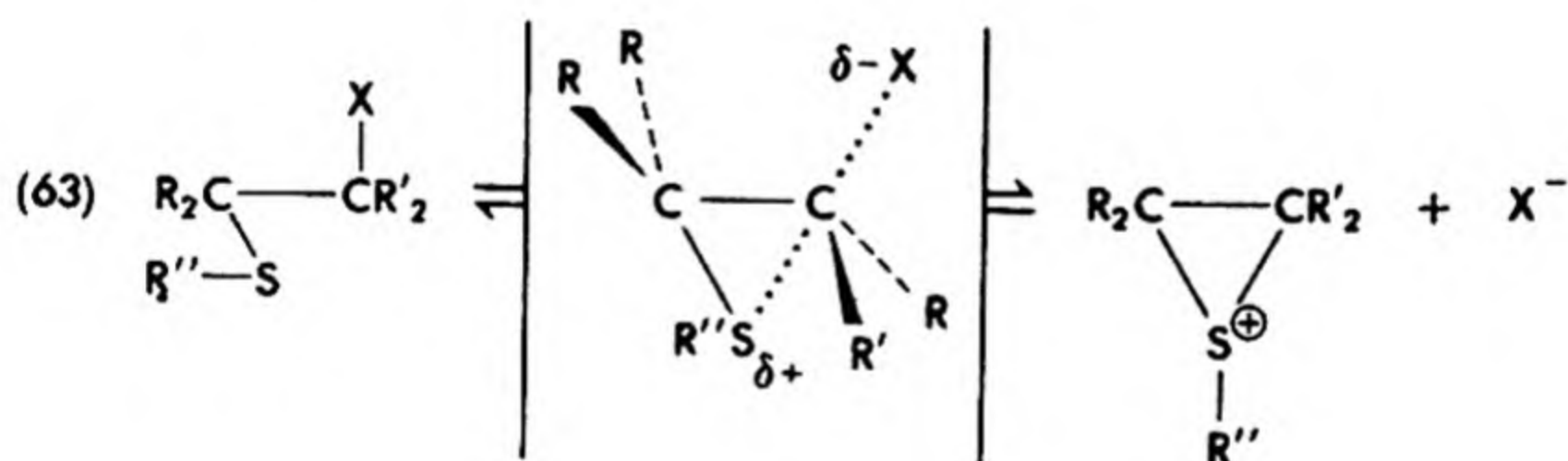
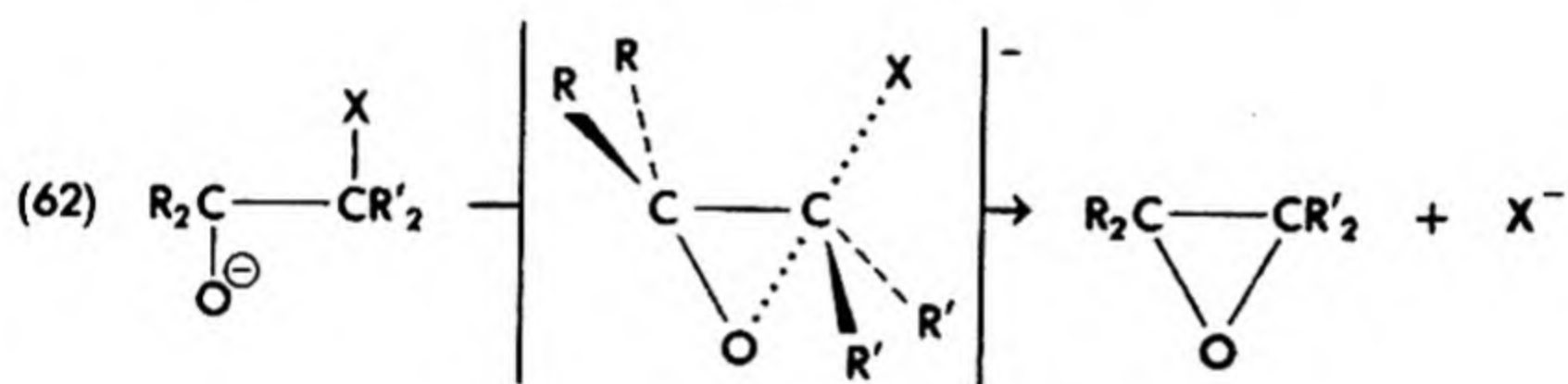
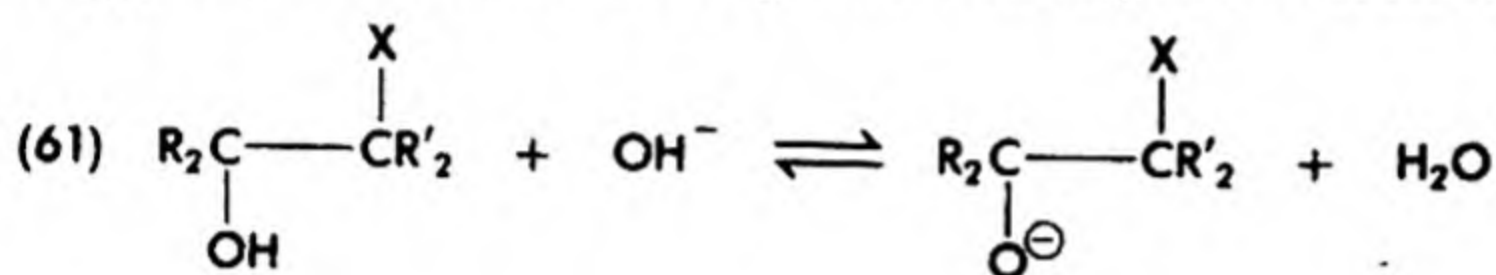


13-4 ELIMINATIONS INVOLVING INTERNAL REPLACEMENTS

Certain elimination reactions are actually internal nucleophilic replacements of one group by another. The most useful of these are reactions which give epoxides or cyclopropanes.

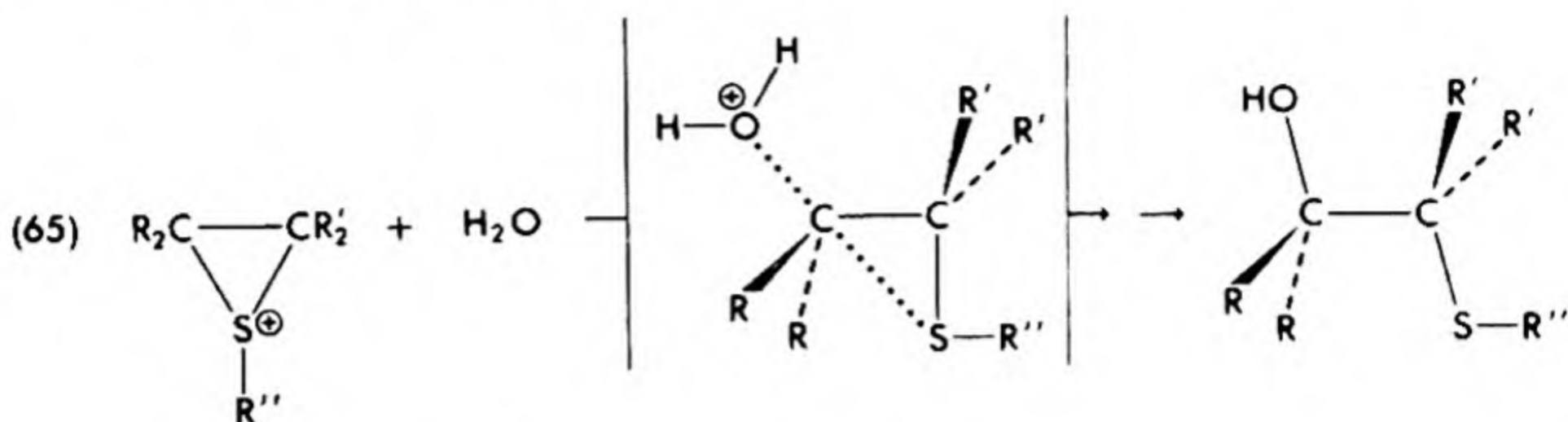
A. Mechanisms

Suitably placed groups, either nucleophilic by nature or rendered so by action of a base, can attack (as usual) the *back* side of a halide-containing carbon atom. While five- and six-membered rings are readily formed thus, surprisingly enough alkene oxides are also readily formed. In fact, three-membered rings participate quite generally, but only those involving oxygen or carbon are usually stable enough to be isolated.



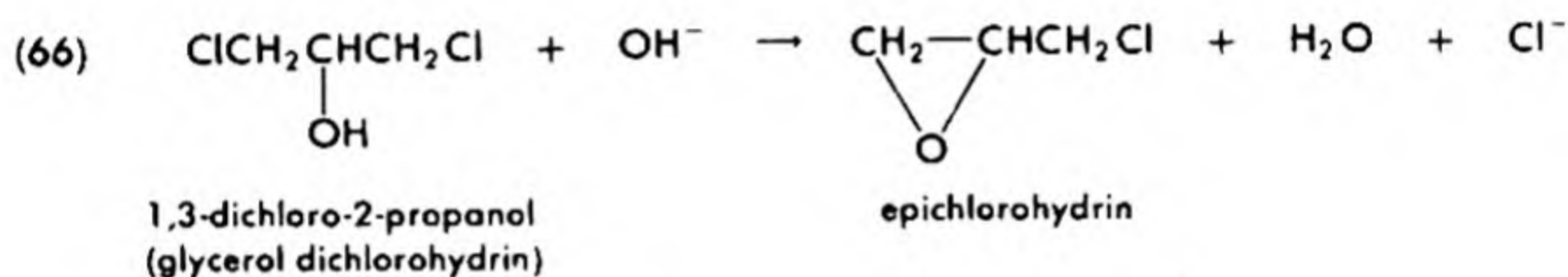
Participation such as eqs. (63) and (64) by one group in a molecule in a replacement of another is called *anchimeric* or *neighboring group* assistance. Its effects are twofold: a large increase in reaction rate (often several

thousand times) unexplainable by electronic or steric factors alone, and net *retention of configuration*. If the ring opens in the opposite sense as the closure, rearrangement may occur.



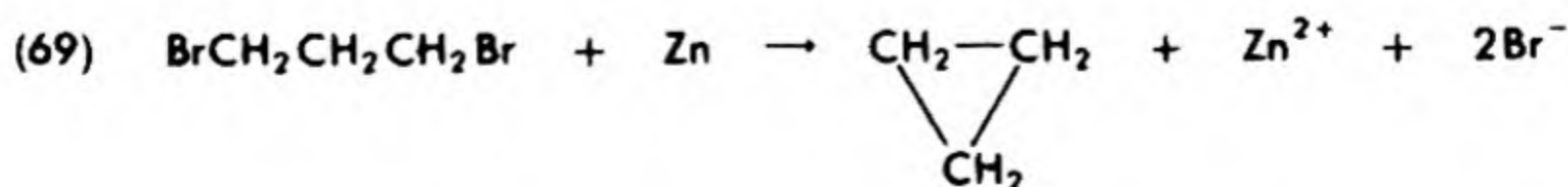
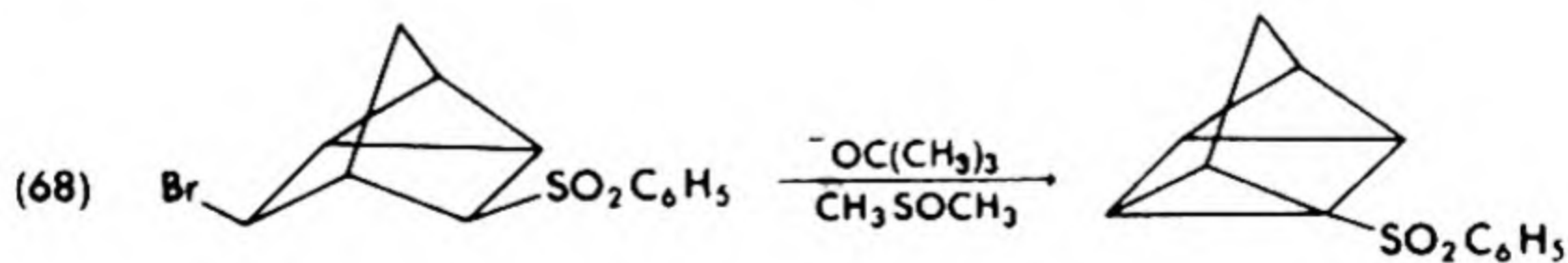
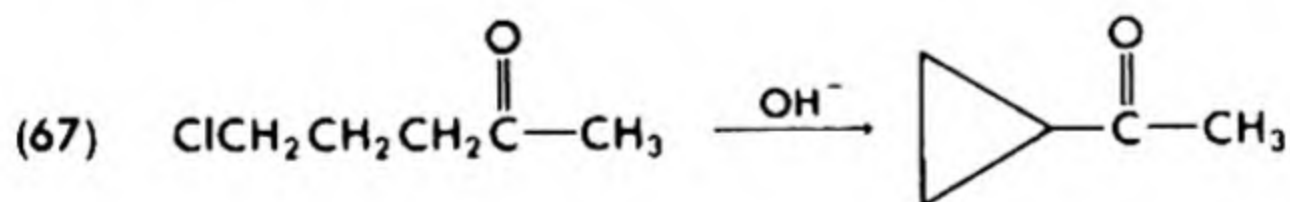
B. Typical Alkene Oxide Preparations

Epichlorohydrin is prepared in 76–81% yields using powdered sodium hydroxide or in 68–72% yields using a calcium hydroxide slurry as dehydrohalogenation agent with glycerol dichlorohydrin (eq. 66).



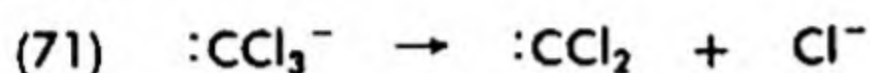
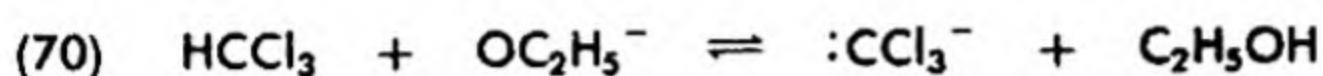
C. Cyclopropane Ring Formation

When a halogen atom is γ to an active hydrogen atom, treatment with base may lead to cyclopropane ring formation. Thus, 5-chloro-2-pentanone gives cyclopropyl methyl ketone (outline 67), and 3-phenylsulfonyl-5-bromotricycloheptane gives 1-phenylsulfonylquadricycloheptane (outline 68). Treatment of trimethylene bromide with zinc gives cyclopropane (eq. 69).



13-5 ALPHA ELIMINATION REACTIONS. CARBENES AND METHYLENES

When chloroform is treated with a strong base, such as sodium ethoxide in ethanol, a portion is converted to the carbanion conjugate base (eq. 70). This can be observed by measuring the rate of deuterium exchange in deuterated solvent. In a much slower reaction, this anion loses chloride ion to give dichlorocarbene (more properly called dichloromethylene) (eq. 71).



Such a reaction, in which both of the atoms or groups eliminated are present on the *same* atom, is called an α -elimination.

A. Structures and Reactivities of Carbenes

Carbene carbon atoms have only six electrons in their valence shells and therefore can be expected to be highly reactive. Some of them, in particular the dihalocarbenes, II, appear to have structures similar to carbonium ions (Figs. 13-2A and 13-3A), whereas others, like diphenylcarbene, III, appear to be biradicals (Figs. 13-2B and 13-3B). Methylene itself may have either structure depending on its mode of preparation and its resulting energy state. For methylene, the biradical is lower in energy and the singlet state, analogous to II, is an excited state.

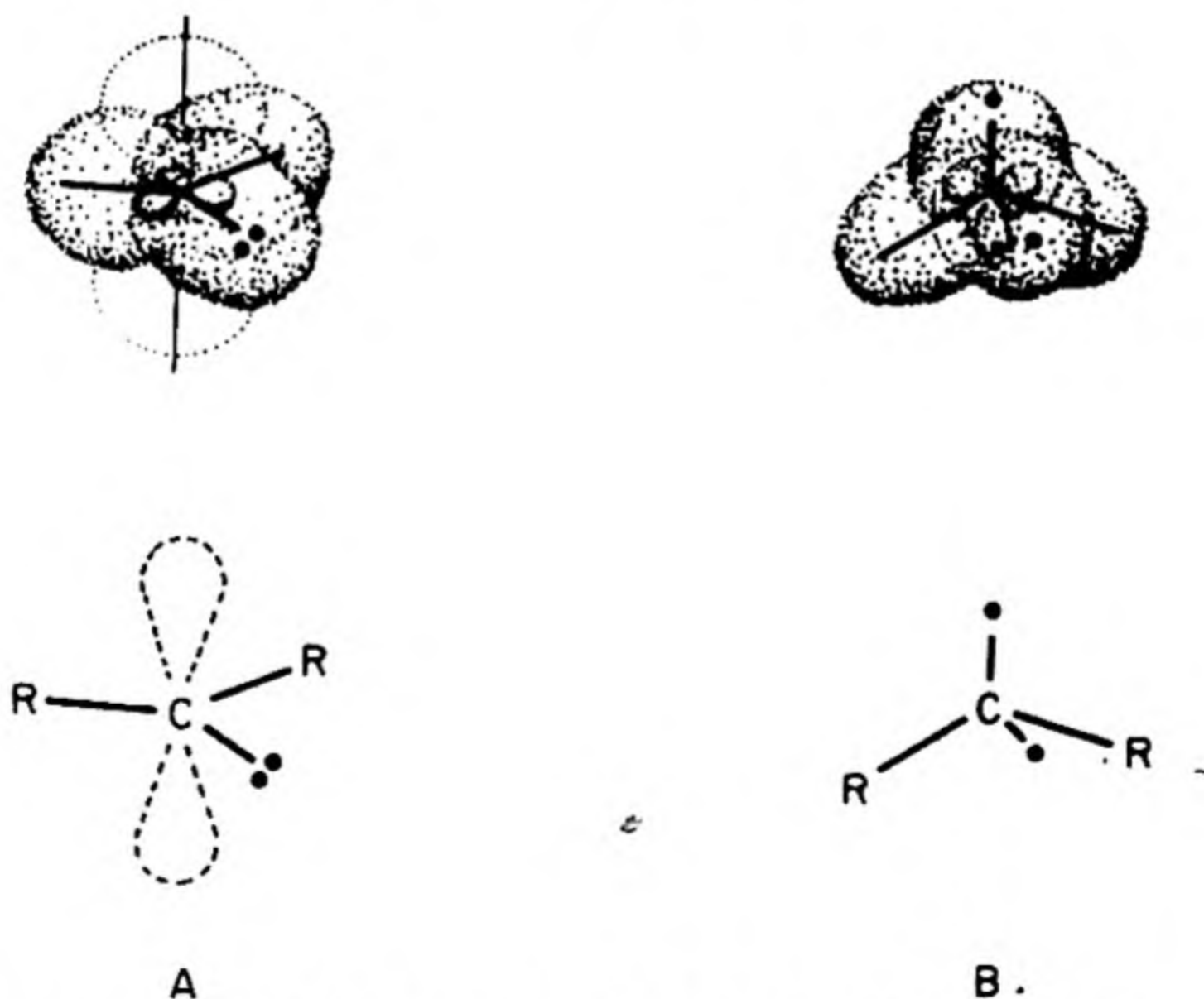


Fig. 13-2. MO Diagrams and MO Clouds for Two Structures of a Methylene (Carbene).

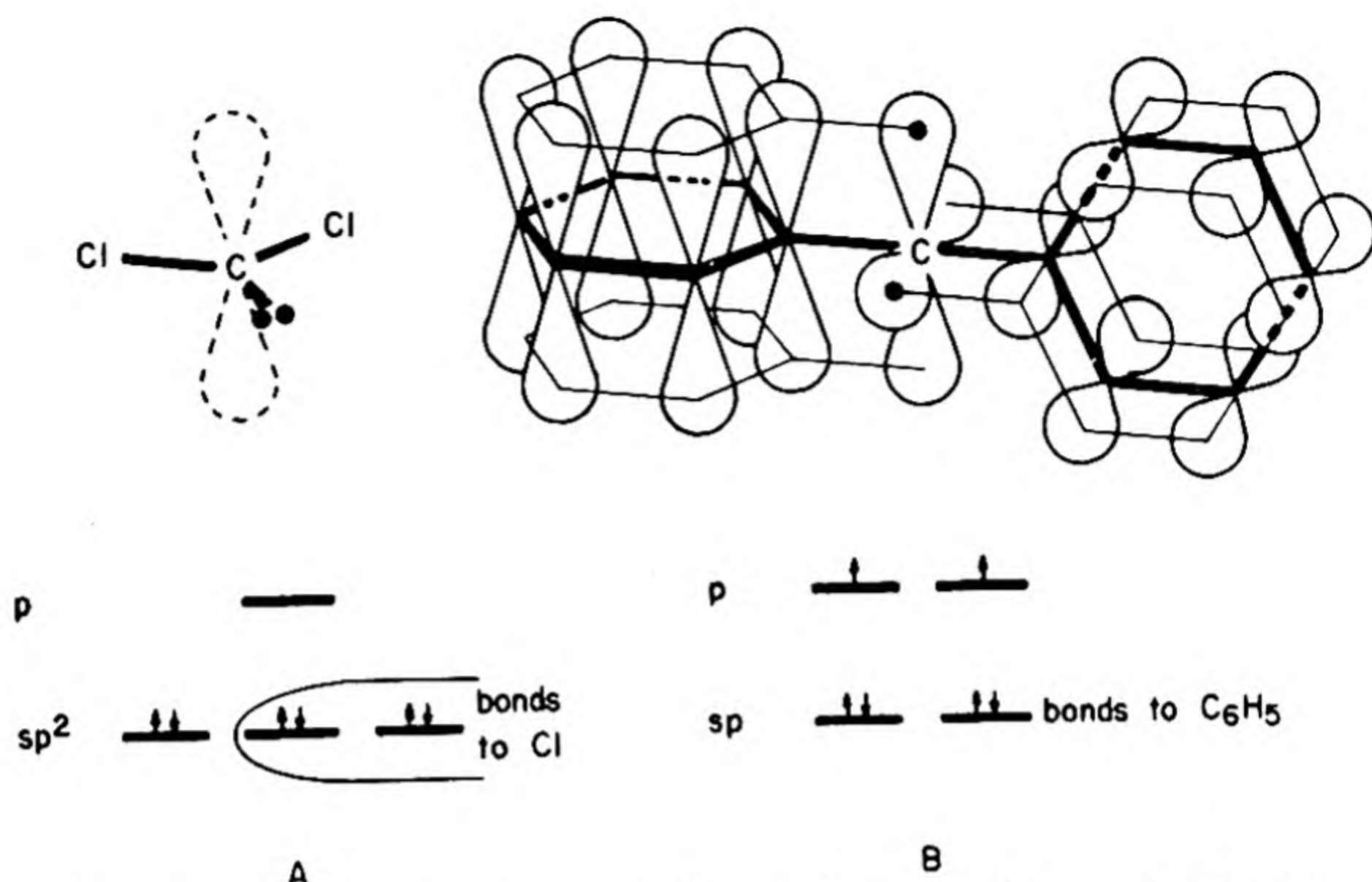
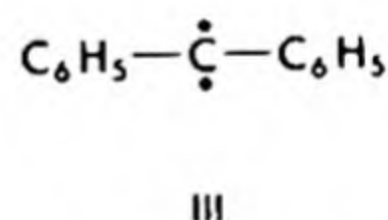
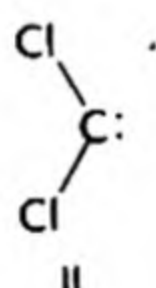
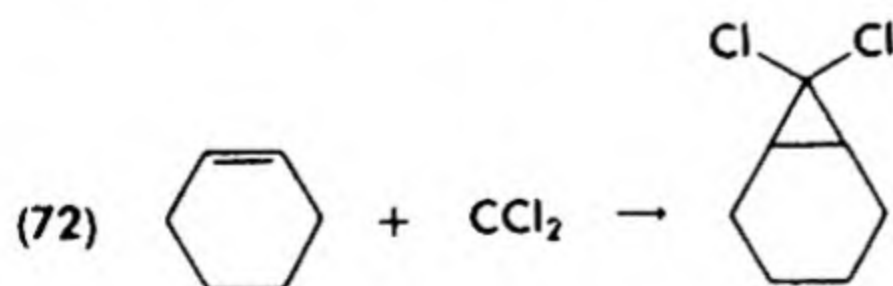


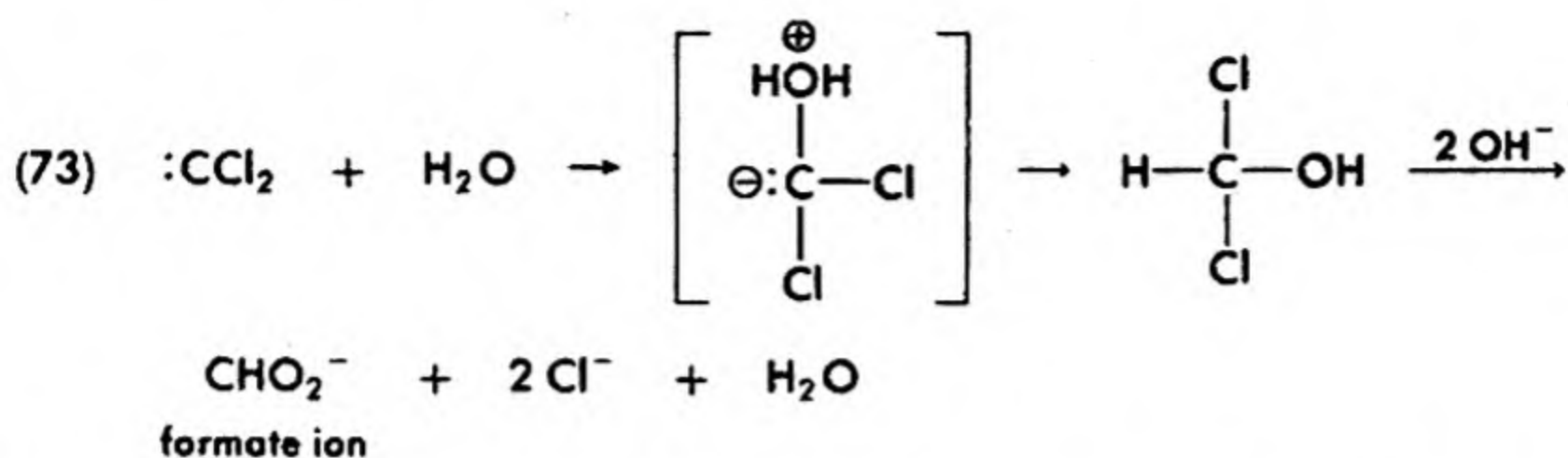
Fig. 13-3. MO Energy Diagrams for Dichloromethylene and Diphenylmethylene. (A) Dichloromethylene, a trigonal electron-deficient species like Fig. 13-2A. (B) Diphenylmethylene, a biradical like Fig. 13-2B. Energy diagram neglects resonance interactions between unpaired electrons and aromatic rings.



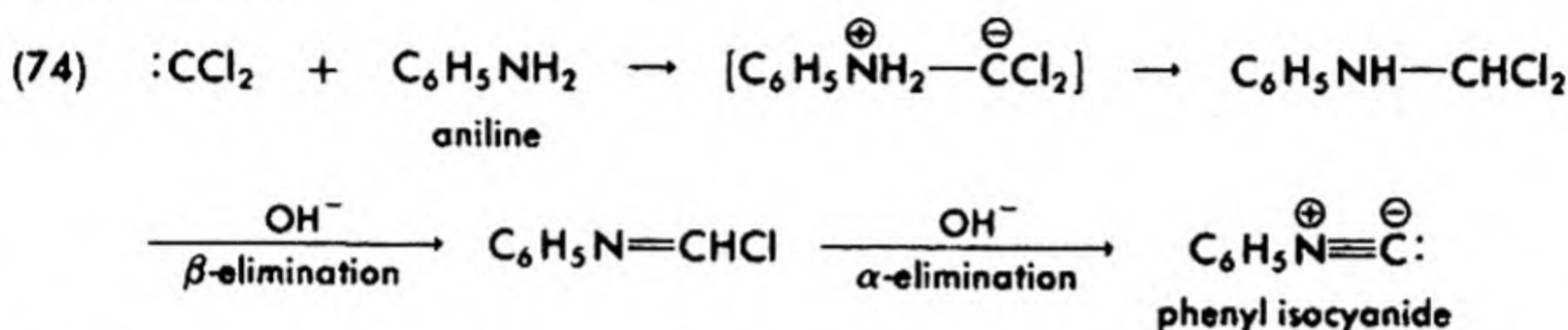
Dichlorocarbene, prepared from chloroform and base, adds rapidly to olefins to give dichlorocyclopropanes. An example of addition to cyclohexene is given in eq. (72). Addition of carbenes to olefins represents a very useful method of synthesis of cyclopropanes.



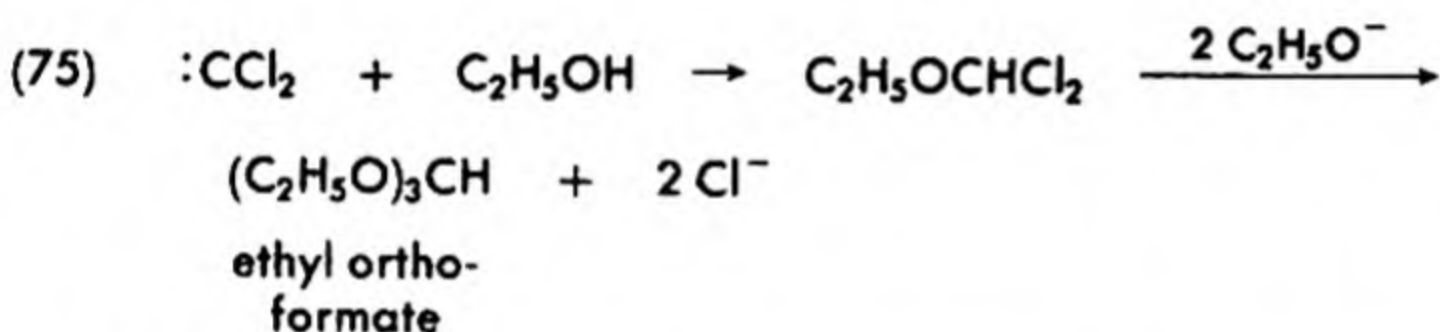
Other reactions of dichlorocarbene from chloroform include hydrolysis to formate ion and reaction with primary amines to give isocyanides (carbylamines; the carbylamine reaction). The former (outline 73) is a side reaction that accompanies other reactions of dichlorocarbene prepared from chloroform. The carbylamine reaction is used as a qualitative



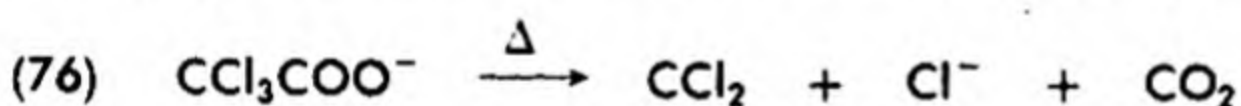
test for primary amines, based on the strong, nauseating odors of the isocyanides.



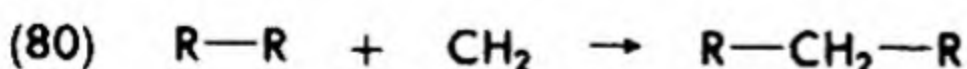
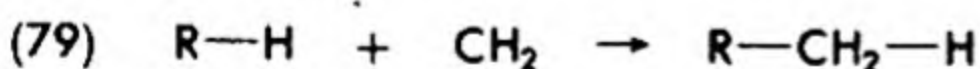
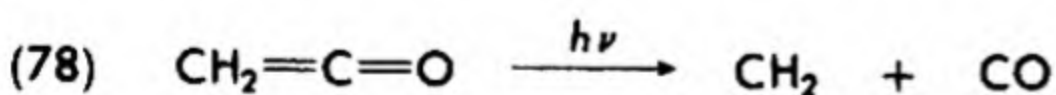
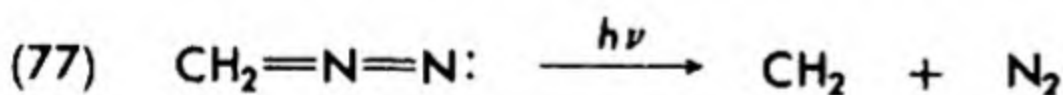
Another industrial preparation that probably goes via dichlorocarbene is orthoformate ester synthesis. This reaction occurs in alcoholic solution of alkali metal alkoxides.



Dichlorocarbene can also be prepared by heating salts of trichloroacetic acid (eq. 76). Carbon dioxide and chloride ion are eliminated.



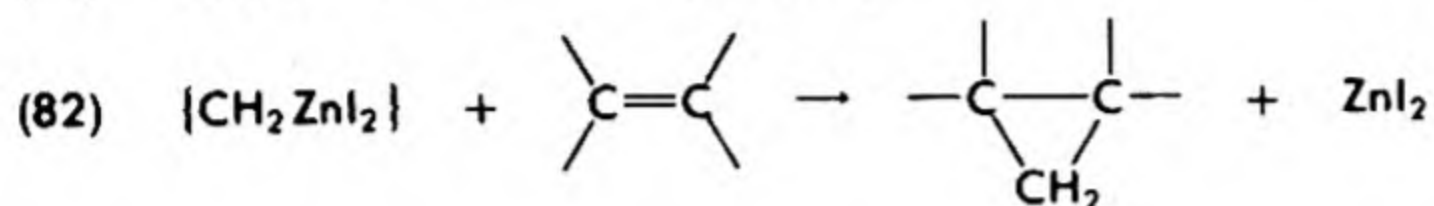
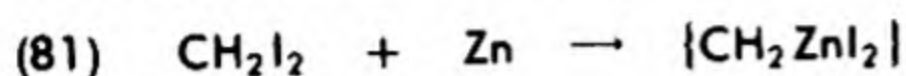
Methylene, CH_2 , can be prepared by photolysis or pyrolysis of diazomethane (eq. 77) or by photolysis of ketene (eq. 78). It is so reactive that it not only adds to double bonds, but also inserts itself into carbon-hydrogen and carbon-carbon bonds (eqs. 79 and 80).



Alkyl- and aryl-substituted methylenes can be prepared from the corresponding diazo hydrocarbons (§24-1) by pyrolysis.

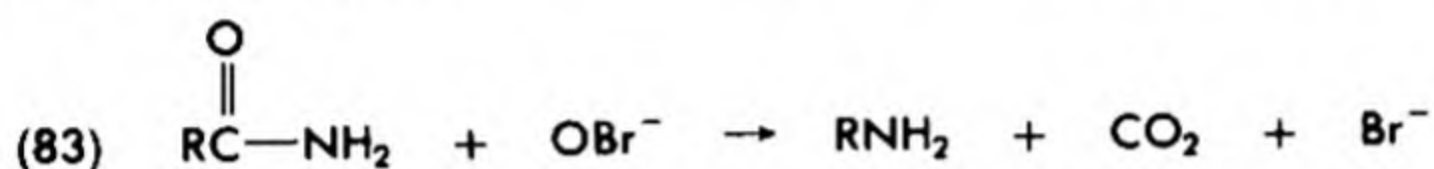
A compound acting like a carbene can be prepared from methylene iodide and zinc. The nature of this compound is not yet clear, but it

adds readily to olefins to give cyclopropanes (eqs. 80 and 82). Other organometallic compounds behave similarly.

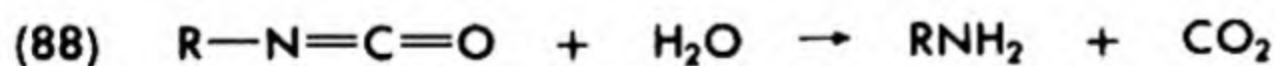
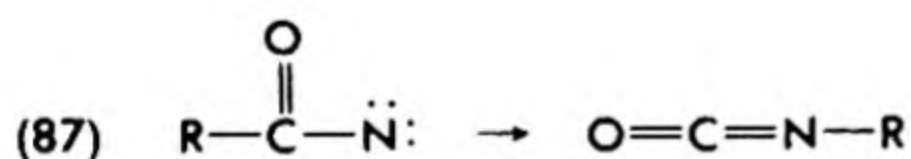
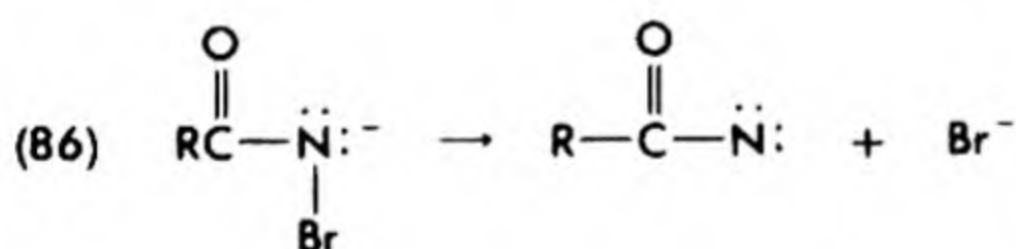
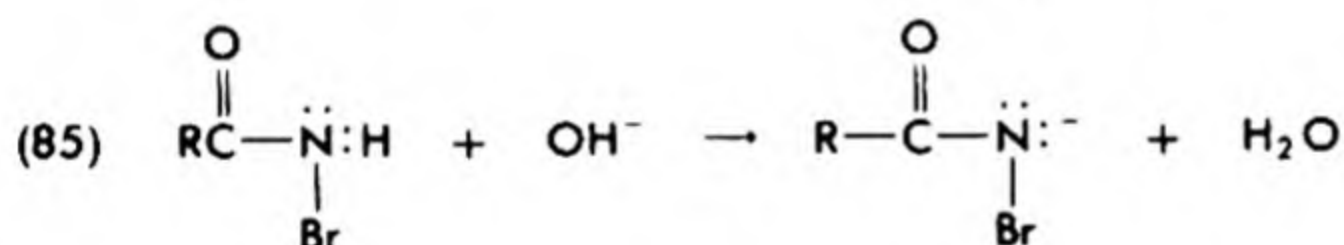
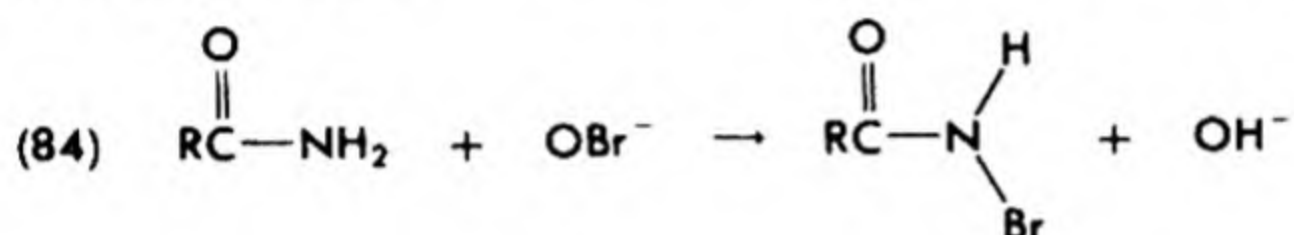


B. Alpha Eliminations from Nitrogen

(1) *The Hofmann Rearrangement.* When an amide is treated with sodium hypohalite, it is converted to an amine with one less carbon atom (eq. 83). This is called the Hofmann reaction or *Hofmann rearrangement*. The mechanistic path of the reaction involves an α -elimination to give an

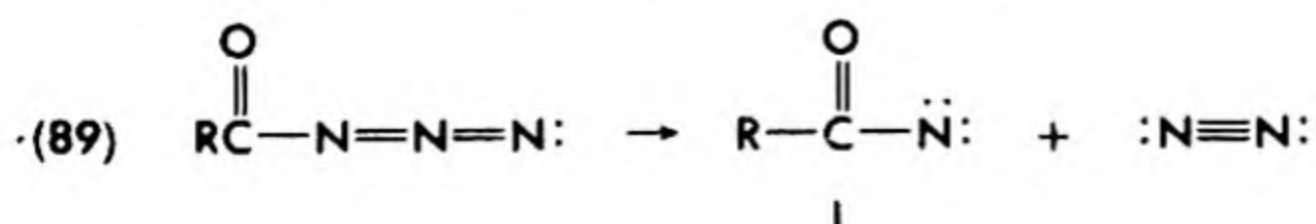


electron-deficient nitrogen atom (eqs. 85 and 86). This species suffers

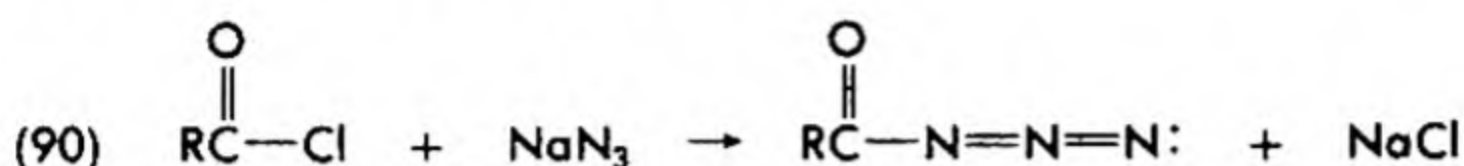


migration of the alkyl or aryl group from carbon to nitrogen to give an isocyanate (eq. 87), which is hydrolyzed to an amine (eq. 88).

(2) *Curtius and Schmidt Degradations.* Important variants of the Hofmann reaction involve the preparation of the key intermediate, I, by decomposition of the acyl azide (eq. 89).



The azide may be prepared from the acid chloride and sodium azide—the *Curtius reaction* (eq. 90). Heating the azide now leads to the isocyanate, which can be isolated.



In the Schmidt procedure, the carboxylic acid is dissolved in sulfuric acid and sodium azide is added carefully. The azide which forms is rapidly transformed to amine (as its sulfate salt) via the reactions in the sequence (eqs. 89, 87, and 88).

SUPPLEMENTARY READINGS

- Banthorpe, D. V., *Elimination Reactions*, Elsevier, Amsterdam (1963).
 Chinoporos, E., "Carbenes. Reactive Intermediates Containing Divalent Carbon," *Chem. Rev.* **63**, 235-255 (1963).
 Cope, A. C., and E. R. Trumbull, "Olefins from Amines—The Hofmann Elimination Reaction and Amine Oxide Pyrolysis," *Org. Reactions*, **11**, 317-493 (1960).
 DePuy, C. H., and R. W. King, "Pyrolytic cis-Eliminations," *Chem. Rev.*, **60**, 431 (1960).
 Fieser, L. F., and M. Fieser, *Advanced Organic Chemistry*, Reinhold, New York (1961), "Carbenes," pp. 536-543.
 Gould, E. S., *Mechanism and Structure in Organic Chemistry*, Holt-Dryden, New York (1959), Chapter 12, "Beta-Elimination Reactions."
 Gould, E. S., *Ibid*, pp. 561-575.
 Hine, J., *Divalent Carbon*, Ronald Press, New York (1964).
 Hine, J., *Physical Organic Chemistry*, 2nd Ed., McGraw-Hill, New York (1962), pp. 484-504.
 Ingold, C. K., *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N.Y. (1953), Chapter VIII, "Olefin-Forming Eliminations."
 Kirmse, W., *Carbene Chemistry*, Academic Press, New York (1964).

QUESTIONS AND PROBLEMS

1. Write equations for the reactions that occur between the substances listed together below. Use structural formulas of organic compounds and indicate essential special conditions. If more than one product is likely to contribute significantly to the yield, write an equation for the formation of each.

- | | |
|---|--|
| a. <i>sec</i> -butyl alcohol and excess concentrated sulfuric acid at 170° | c. diethyldimethylammonium iodide heated |
| b. <i>tert</i> -butyl bromide and hot, concentrated sodium hydroxide solution | d. trimethyl- <i>n</i> -butylammonium hydroxide heated |

- | | |
|---|---|
| e. ethylene dichloride and alcoholic potassium hydroxide | h. octanoyl azide heated |
| f. 2,3-dibromobutane and magnesium. | i. urea, sodium hypobromite, and sodium hydroxide |
| g. 2-chloro-3-butanol and concentrated or powdered sodium hydroxide | j. <i>trans</i> -2-butene and diazomethane heated |

2. Show how the following syntheses can be accomplished in good yield. Indicate reagents and essential special conditions.

- | | |
|--|--|
| a. 2°-butyl bromide from <i>n</i> -butyl alcohol | c. methylacetylene from isopropyl alcohol |
| b. 1,3-cyclooctadiene from cyclooctane | d. 2-butene from ethanol |
| | e. propylene oxide from <i>n</i> -propyl alcohol |

3. Write an equation showing how anchimeric assistance could intervene in the hydrolysis of 2-dimethylamino-1-chloropropane. What might occur if the water molecule attacked the intermediate on the middle carbon atom?

4. Indicate a possible role of dichloromethylene in the formation of phenylcarbylamine (phenyl isocyanide) from aniline, chloroform, and sodium hydroxide.

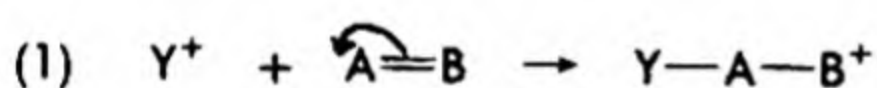
14

Electrophilic Additions to Carbon-Carbon Multiple Bonds

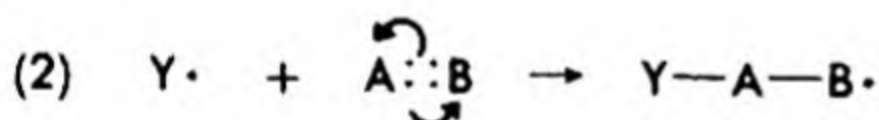
14-1 GENERAL REACTIVITIES OF MULTIPLE BONDS

Multiple bonds, which contain readily polarizable π electrons (§4-1G(3), §7-2), may react with electrophiles to give cationic species (eq. 1), with radicals to give new radicals (eq. 2), or with nucleophiles to give anionic species (eq. 3). This chapter is limited to those reactions of carbon-carbon double and triple bonds in which the initiating step involves the donation of the π electron pair in the multiple bond to an electrophilic reagent. The other two types are discussed in Chapters 15 and 22, respectively.

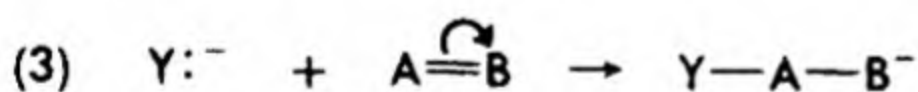
Electrophilic addition



Free radical addition

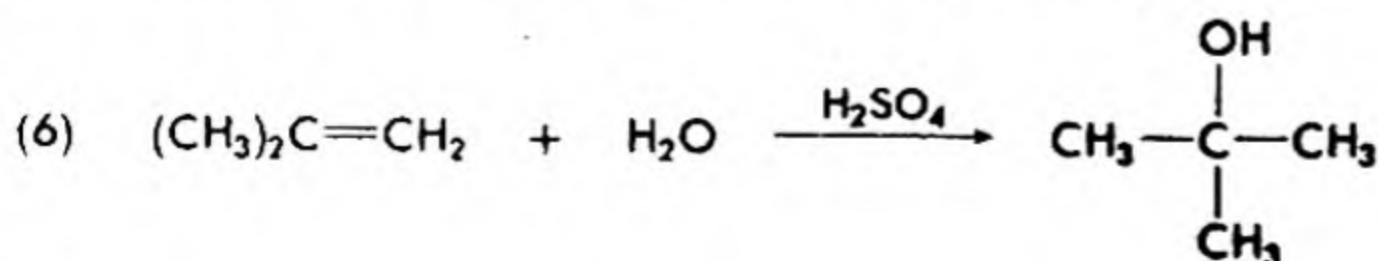


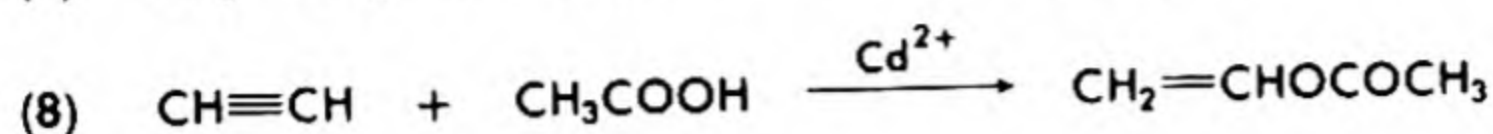
Nucleophilic addition



14-2 ELECTROPHILIC ADDITIONS

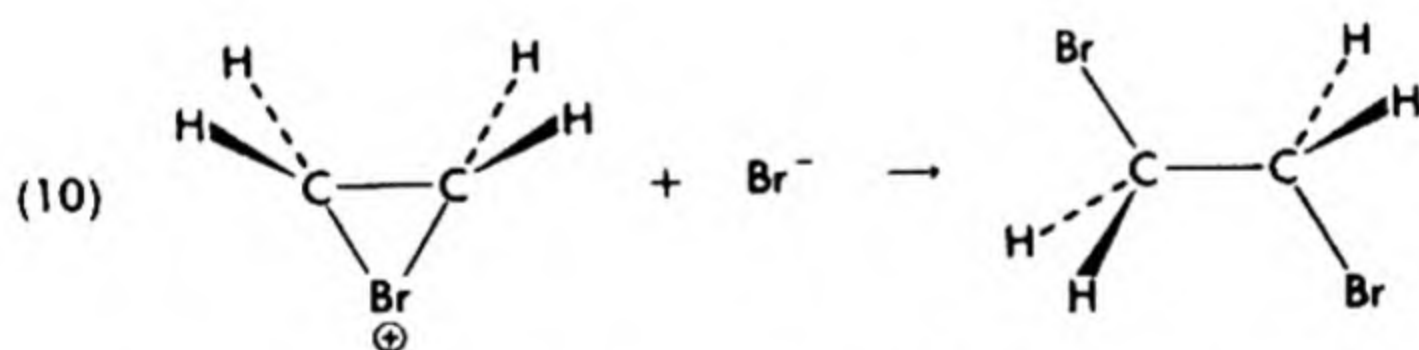
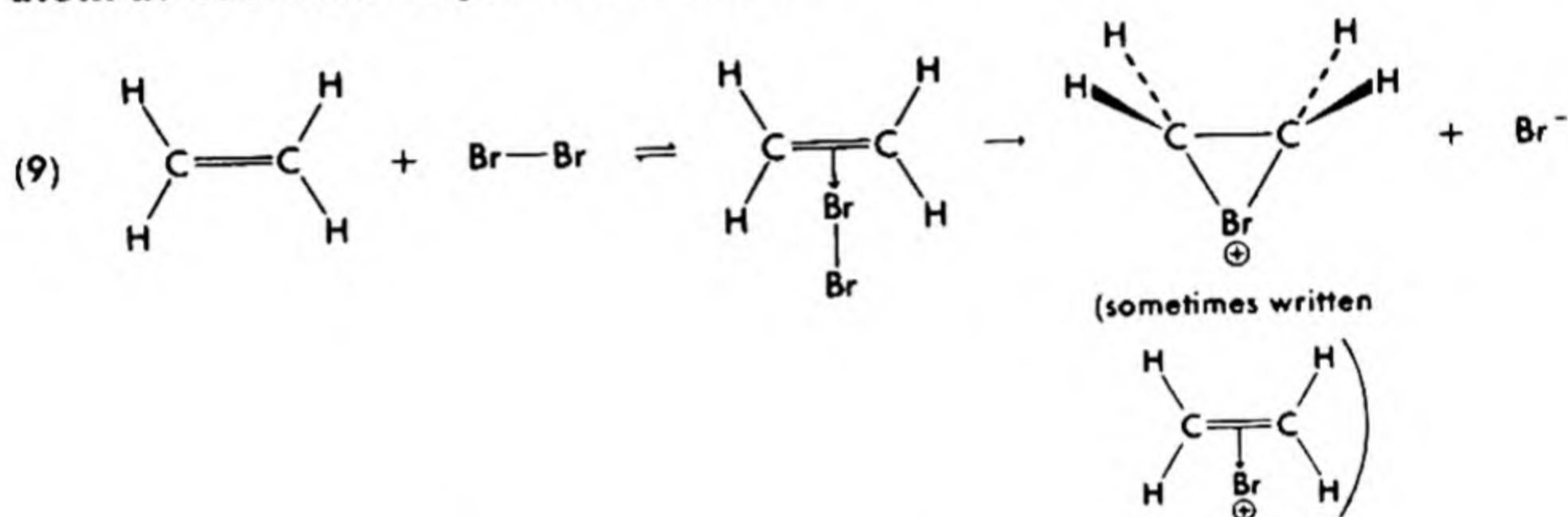
Electrophilic additions include addition to olefins of chlorine, bromine, and strong protonic acids, as well as acid-catalyzed addition of water, alcohols, organic acids, and weak inorganic acids, and certain similar additions to acetylenes. Some examples are given in eqs. (4) to (8).



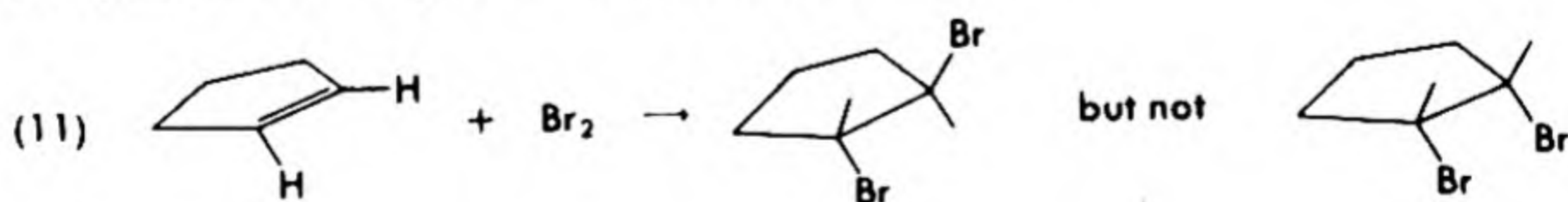


A. Mechanisms of Electrophilic Additions

The first step of electrophilic addition of bromine to a double bond is probably the formation of a π complex (eq. 9 and Fig. 14-1A) in which the bromine molecule may be assumed to be embedded in one lobe of the π electron cloud of the double bond. This complex then cleaves to a bromonium ion (Fig. 14-1B) and bromide ion. The latter attacks the former by a process involving inversion of configuration of the carbon atom at which the displacement occurs.



It should be noted that this mechanism leads to *trans* addition of bromine; that is, one part of the bromine molecule adds above the plane of the olefin atoms and the other below it. This can be demonstrated with appropriately substituted olefins, such as cyclopentene, where addition of bromine is stereospecific and *trans* (eq. 11).



As the formation of the bromonium ion is the slow step, the rate of bromination of simple olefins depends upon the concentration of olefin and of bromine. These kinetic results encompass either the path shown or one in which the π complex, which is written as an intermediate above, is instead a transition state. It is not possible to distinguish the two kineti-

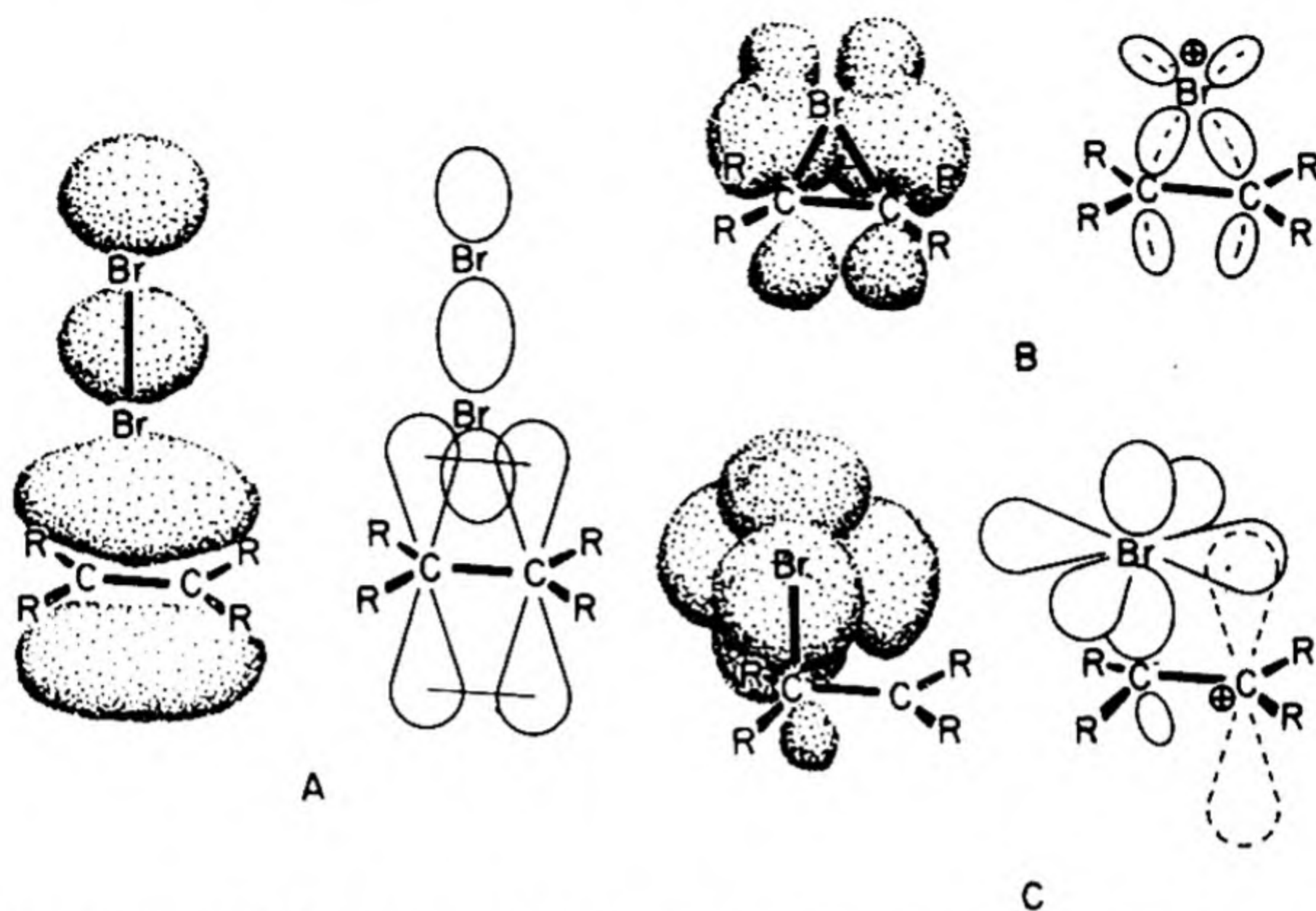
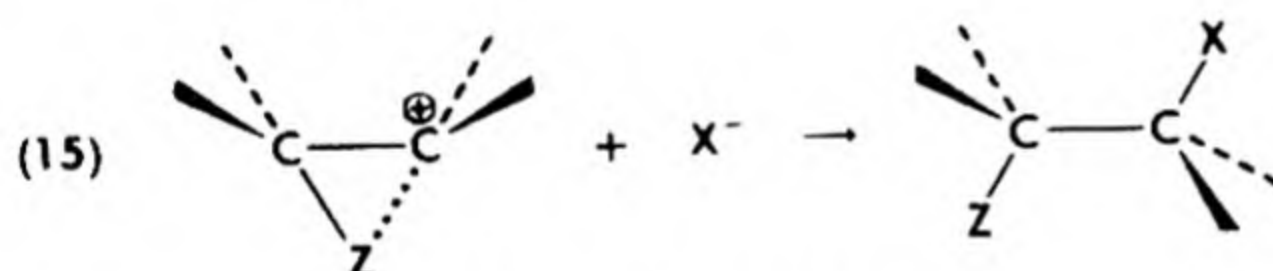
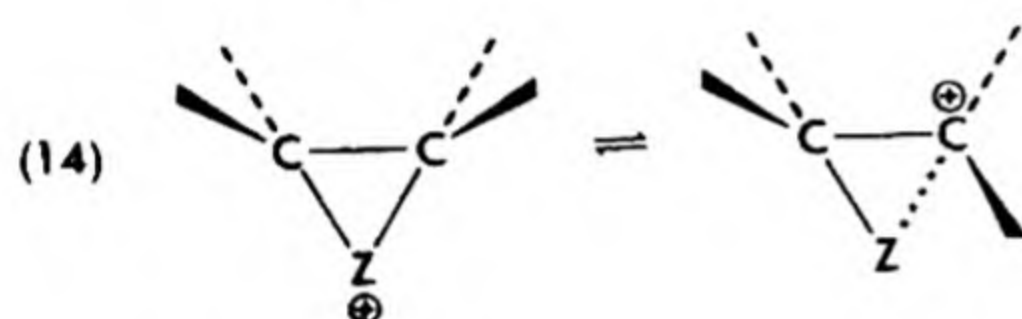
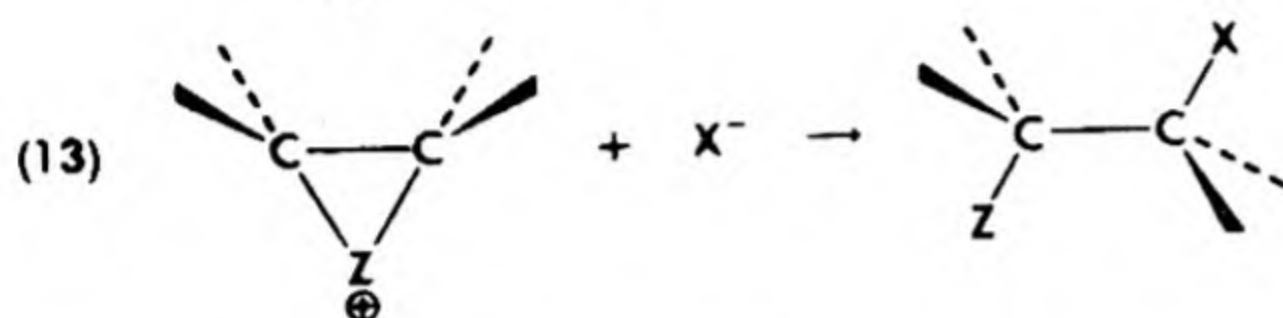
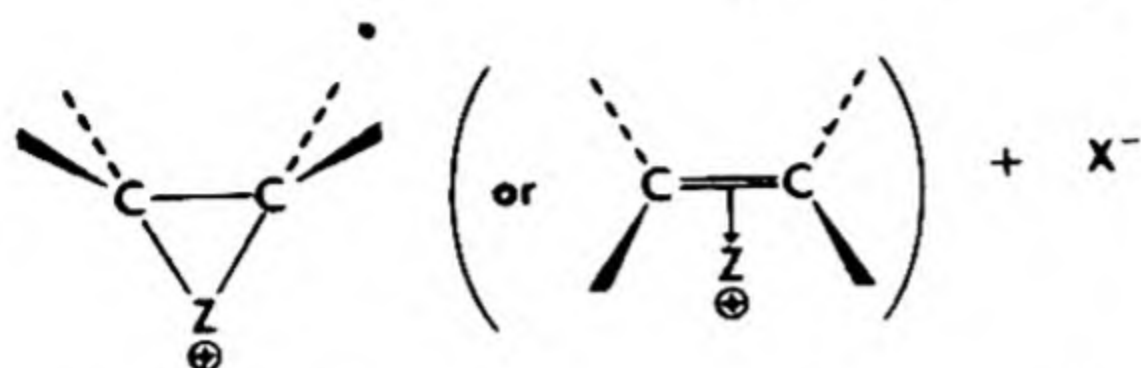
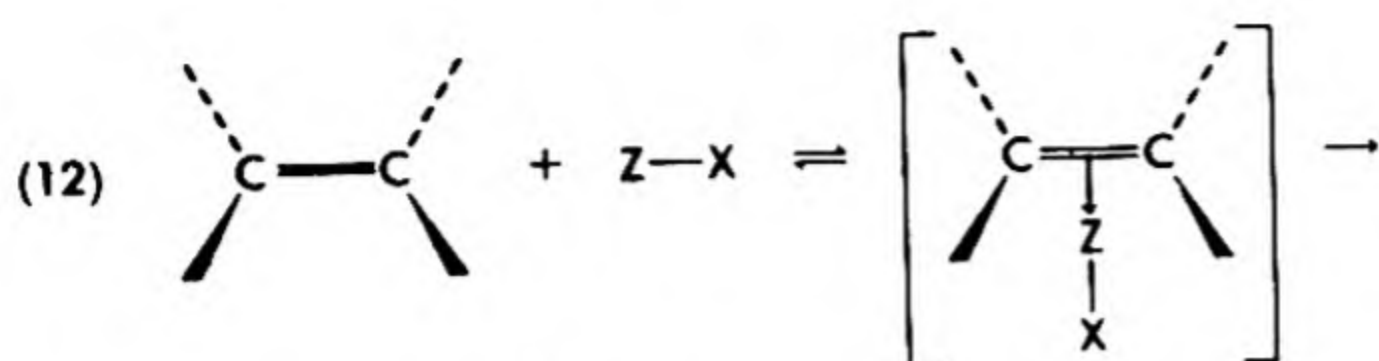


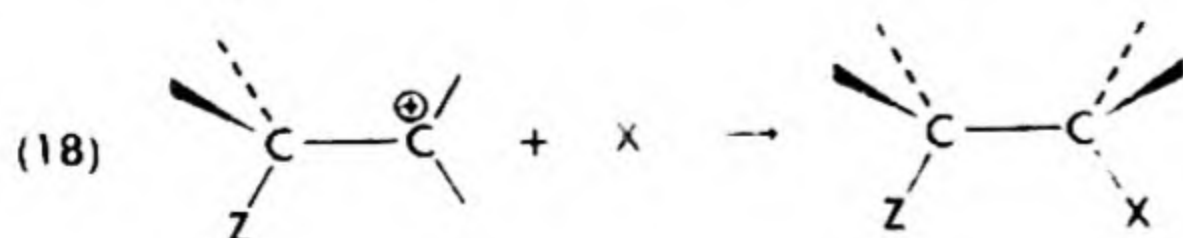
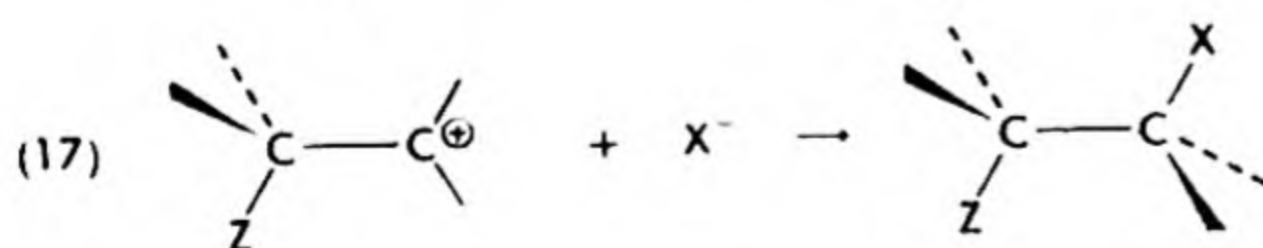
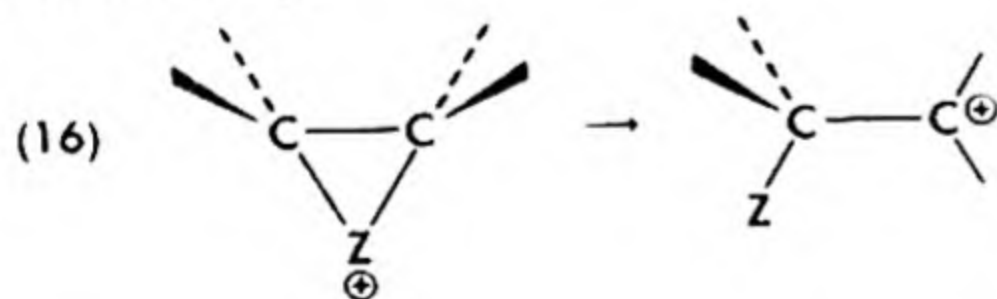
Fig. 14-1. MO Clouds and MO Formulas Representing Various Derivatives of π Systems. (A) π complex, (B) Cyclic onium ion, (C) Carbonium ion of tight ion-dipole type.

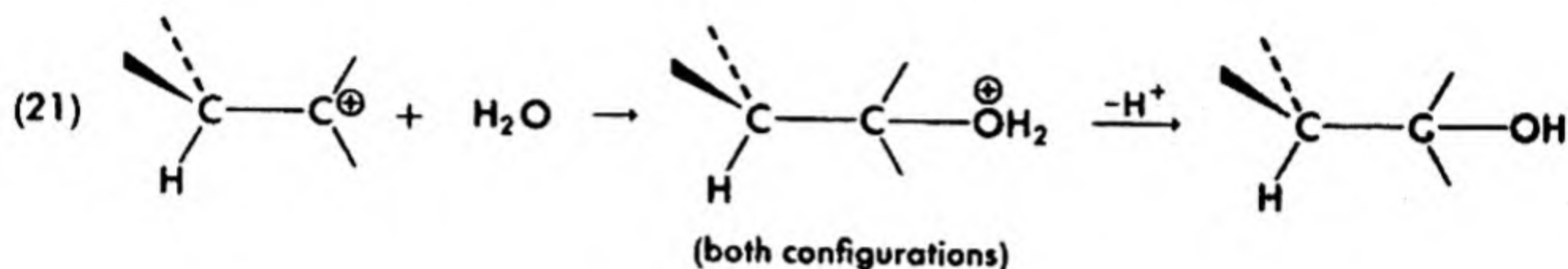
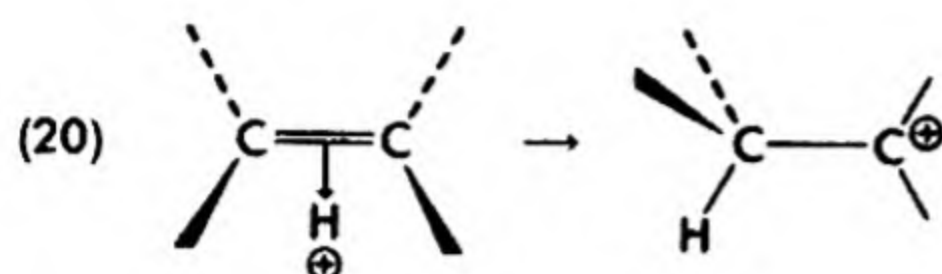
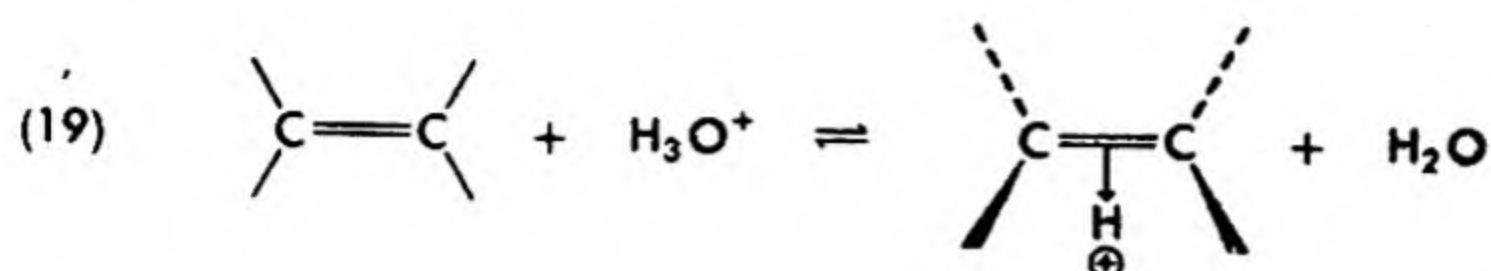
cally, but iodine, which does not ordinarily form diiodides with olefins, does in fact form π complexes which can be detected spectroscopically.

If we generalize the mechanism given above for the addition of any reagent, $Z-X$, in which Z is the electrophilic portion of the reagent, we have eqs. (12) and (13). One might assume that the second portion of the reaction (i.e., that represented by eqs. (10) and (13), which are clearly nucleophilic displacement reactions) are of the direct displacement type. However, this does not appear to be the case. Apparently, the ring opening utilizes the carbonium ion mechanism, with a rather tight ion-dipole effectively preserving the stereochemistry in the bromine addition. These reactions are shown in eqs. (14) and (15). We have noted (§12-1B(2)) that carbonium ion reactions may give complete inversion in those cases where the intimate ion pair reacts with a nucleophile before dissociating to symmetrically solvated ions. A similar scheme is formulated for stereospecific *trans* addition, as with bromine, except that an ion-dipole is involved rather than an ion pair. It might be anticipated that as the cation- Z interaction becomes weaker, or as X becomes a poorer nucleophile, or as the solvent polarity becomes greater (so as to slow down reactions of cations with nucleophiles), the ion-dipole interaction will be broken and a solvated carbonium ion will result (eq. 16). In such cases one does not observe stereospecific *trans* addition, but both *cis* and *trans* addition (eqs. 17 and 18). Chlorine addition is often not stereospecific and addition of



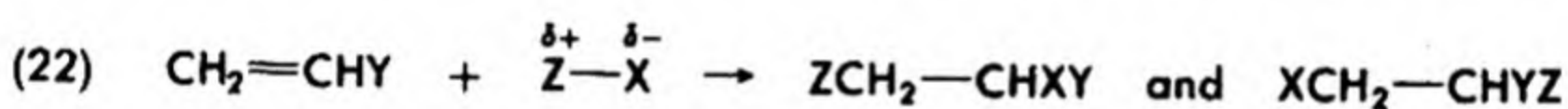
acids, water, or alcohols is generally nonstereospecific. Thus, for hydration of an olefin, the mechanism in eqs. (19) to (21) appears to explain the results. Although the π -complex intermediate (eqs. 19 and 20), is widely accepted, in many cases the protonation probably forms the carbonium ion directly.



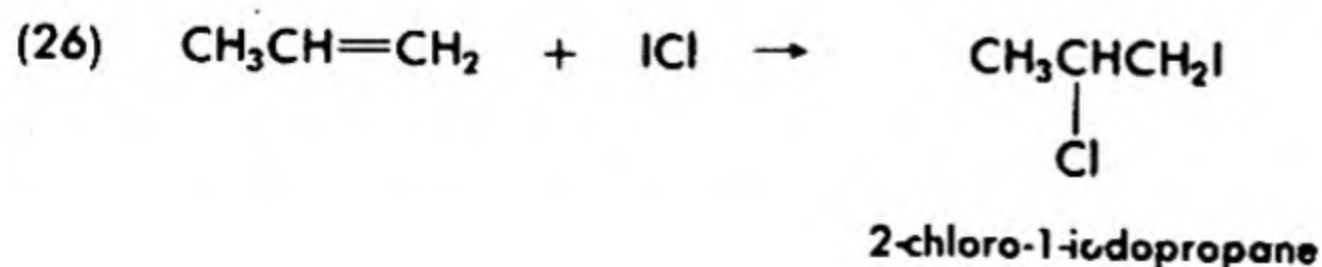
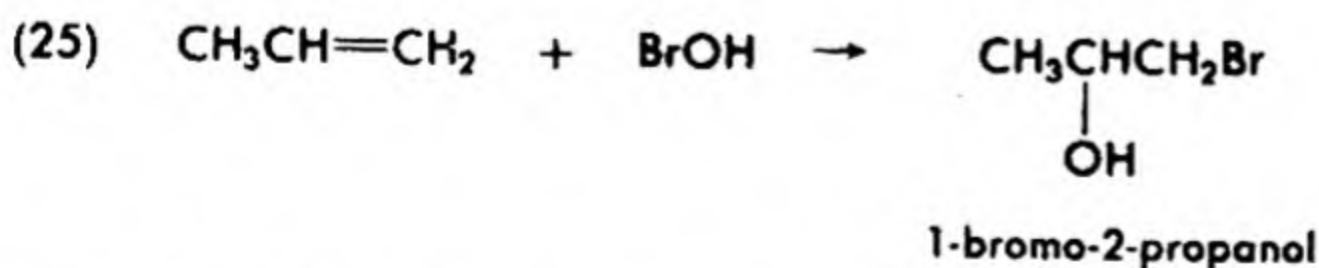
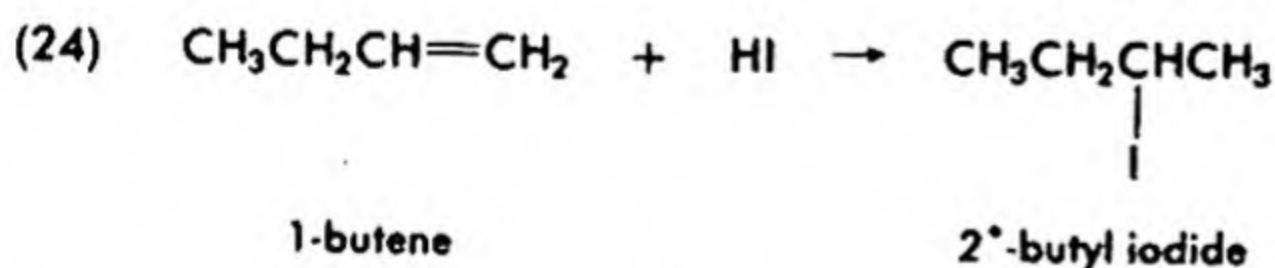
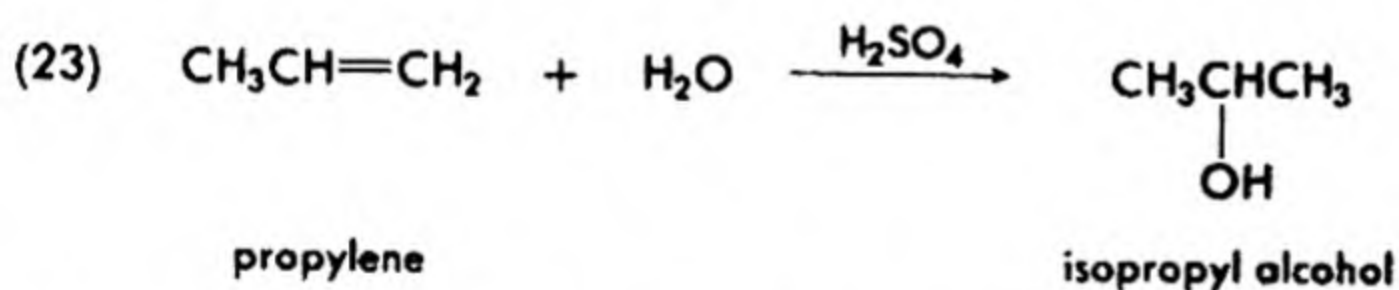


B. Markovnikoff's Rule

In 1896, Vladimir Markovnikoff published an empirical rule that describes the results to be expected upon the addition of unsymmetrical reagents to unsymmetrical olefins (outline 22). The rule, as somewhat



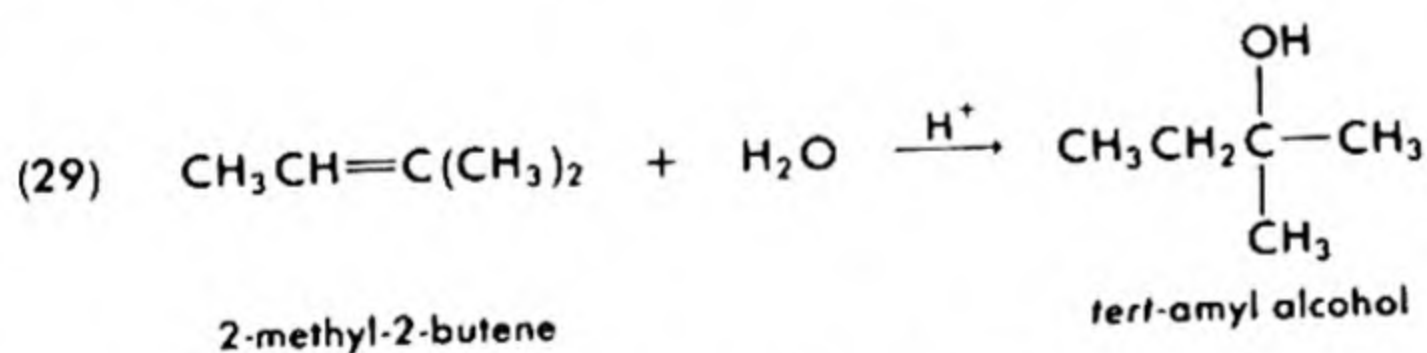
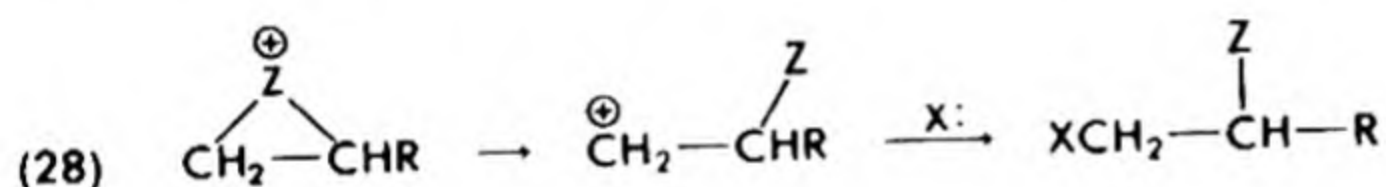
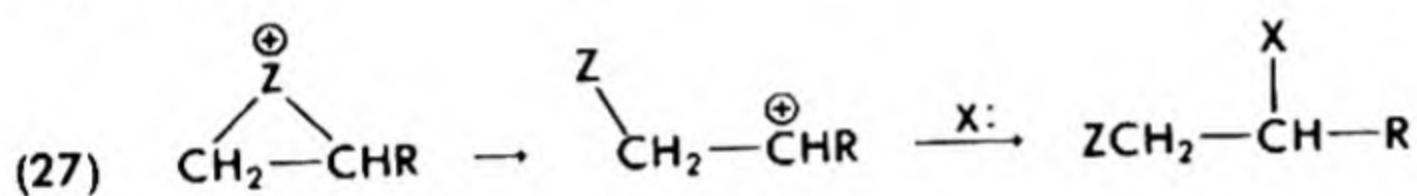
expanded, is that the positive portion of a reagent (i.e., the electrophilic atom) attaches itself to the olefinic carbon atom which already contains the larger number of hydrogen atoms. Some examples of this are given in eqs. (5), (6), (23), (24), (25), and (26).



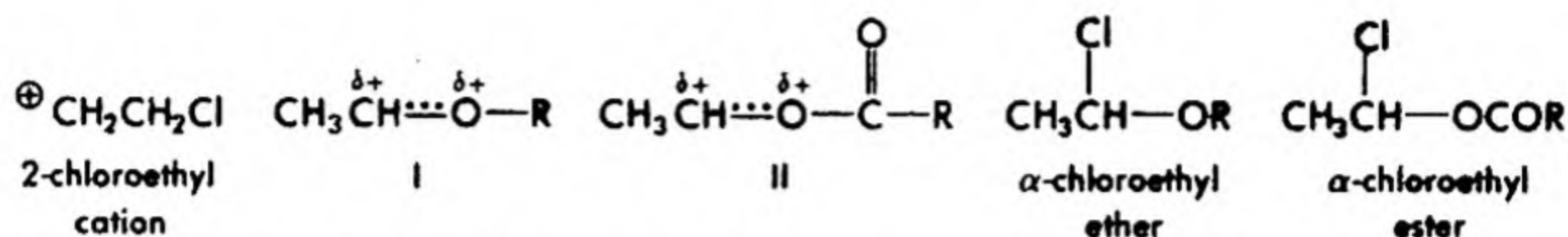
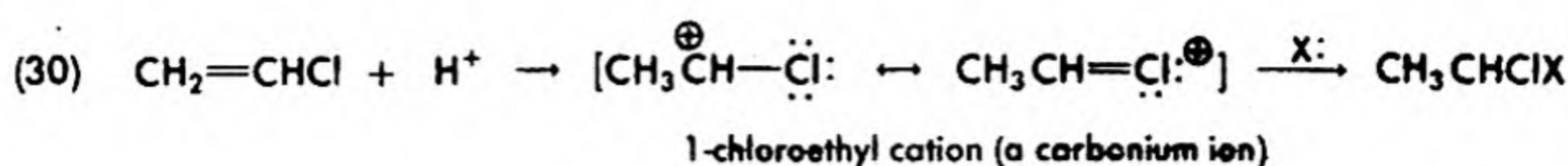
It should be emphasized that addition often occurs in both directions, but that the major portion of the product forms according to Markovnikoff's rule. The rule applies to electrophilic and *not to free radical* addition, as we shall see later. The rule also breaks down when the C=C bond is con-

jugated with an electron-withdrawing group (e.g., $-\overset{\text{O}}{\parallel}{\text{C}}-$, $-\text{C}\equiv\text{N}$, etc.).

The explanation for Markovnikoff's rule is quite straightforward. The direction of addition depends entirely upon the relative stabilities of the two possible carbonium ion intermediates (outlines 27 and 28). We have noted already that secondary carbonium ions are more stable than primary, hence the rate of the first part of eq. (27) will be greater than the corresponding rate in eq. (28), so that the more positive (electrophilic) group ends on the terminal atom and the nucleophilic portion on the more substituted carbon atom. As tertiary carbonium ions are more readily formed than secondary, 2-methyl-2-butene hydrates to *tert*-amyl alcohol (eq. 29).



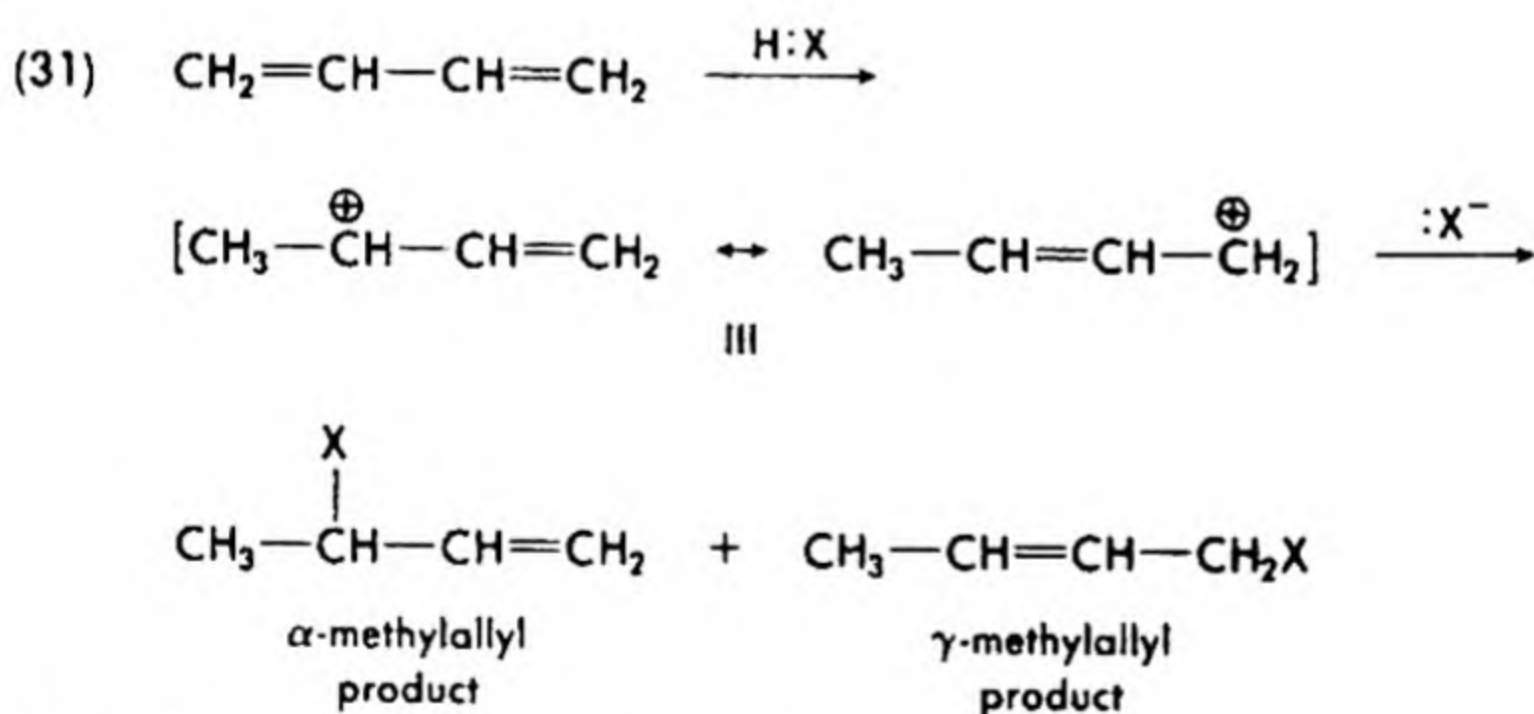
The direction of electrophilic addition reactions to olefins is thus controlled by the relative stabilities of the carbonium ions which result by addition of a positive ion from the electrophile and not by the polarity of the olefin substrate. (This assumes that the stabilities of the transition states for formation of carbonium ions reflects the relative stabilities of those carbonium ions.) Carbonium ions are stabilized (§12-1B(4)) not only by alkyl substituents but also by other electron-donating groups and in particular by groups which donate electron pairs by conjugation. Thus, addition of a cation, for example, a proton, to vinyl chloride gives the 1-chloroethyl cation, which is stabilized by resonance, rather than the 2-chloroethyl cation which is not. Similarly, vinyl ethers and esters lead to protonation to give I and II, which ultimately yield α -chloroethyl ethers and α -chloroethyl esters.



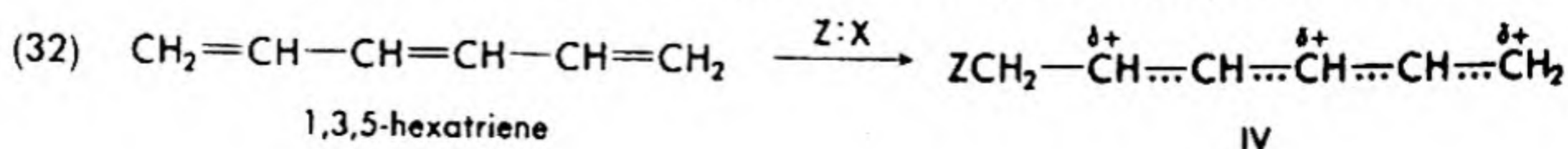
The reactivities of olefins with electrophiles, like all such reaction rates, depend upon the relative stabilities of the transition states for the rate-determining step (in this case usually the formation of the carbonium ion) and those of the starting olefins and reagent. As the olefin is the nucleophile, one might anticipate that the rates would parallel electron availability in the olefin. Thus, propylene is faster than ethylene, which in turn is faster than vinyl bromide, in agreement with effects of electron-donating and electron-attracting groups upon electron availability in the olefin.

C. Additions to Conjugated Systems

When an electrophile adds to a conjugated diene, addition occurs in the direction such as to lead a resonance-stabilized allylic cation. Thus, for example, addition of a proton to butadiene (eq. 70) gives the cation, III, which, as noted before (§12-1B(5)), coordinates with nucleophiles at either one of the two positive centers to give a mixture of the α - and γ -methylallyl coordination products.



The process of addition to two vicinal atoms (e.g., to give α -methylallyl product) is termed 1,2-addition, while that to the first and fourth atom in a conjugated diene (e.g., to give γ -methylallyl product) is called 1,4- or conjugate addition. Conjugated trienes (e.g., 1,3,5-hexatriene) may give 1,2-, 1,4-, and 1,6-addition products, as the intermediate carbonium ion, IV, has the positive charge distributed over three alternate carbon atoms, so that the nucleophile may coordinate with any of these positive centers.



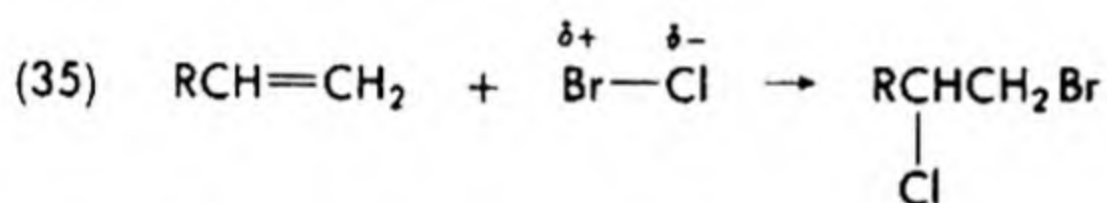
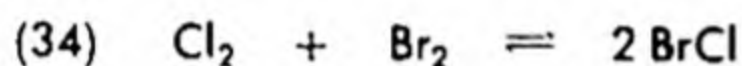
synthetic usefulness of acetylenes and olefins derives from the fact that the function encompassing two carbon atoms can be used for changing positions of functional groups or for introducing two functional groups into the molecule.

The availability of olefins from cracking of petroleum makes them important chemical raw materials for alcohols, sulfates, dihalides, and many other compounds.

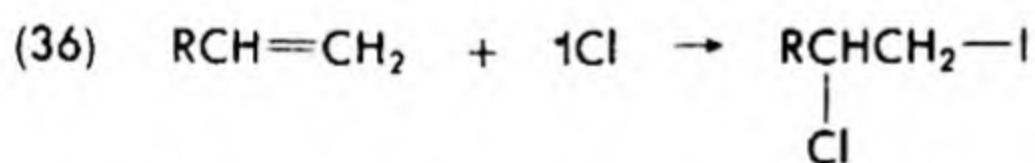
Yields of bromine-addition compounds from such diverse unsaturated compounds as allyl bromide, benzalacetophenone, cyclohexene, and fumaric acid are often close to quantitative.

Addition of chlorine to unsaturated compounds, such as methyl acrylate, *cis*- and *trans*-2-butenes, and 3-hexene at very low temperatures and efficient mixing of chlorine also gives good yields of addition products. Light and peroxides must be avoided, since these lead to side reactions.

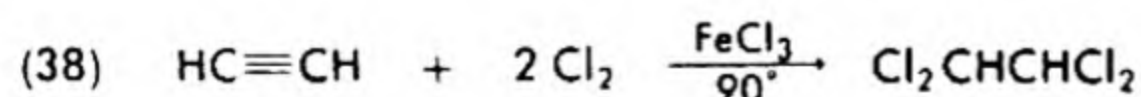
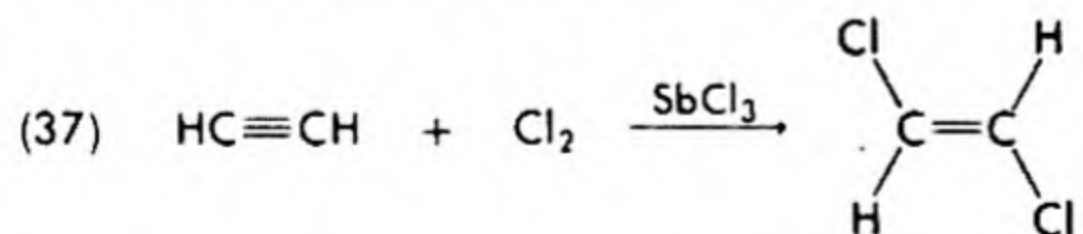
Mixed halogens are also useful reagents. They add as polar molecules. The reagents are prepared by mixing exactly equivalent amounts of the two halogens.



Addition of iodine chloride or iodine bromide to unsaturated linkages is the basis of a quantitative method of estimating the degree of unsaturation of a fat. Iodine itself does not add to olefinic bonds by the electrophilic mechanism.

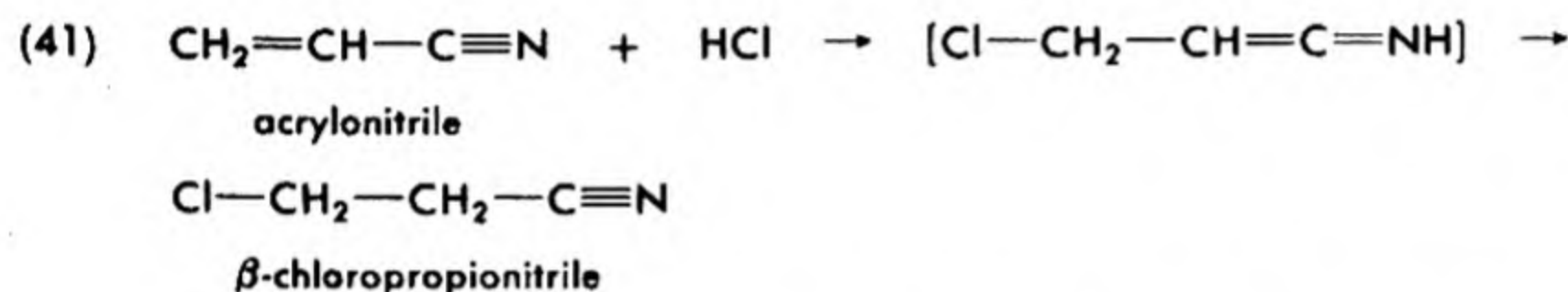
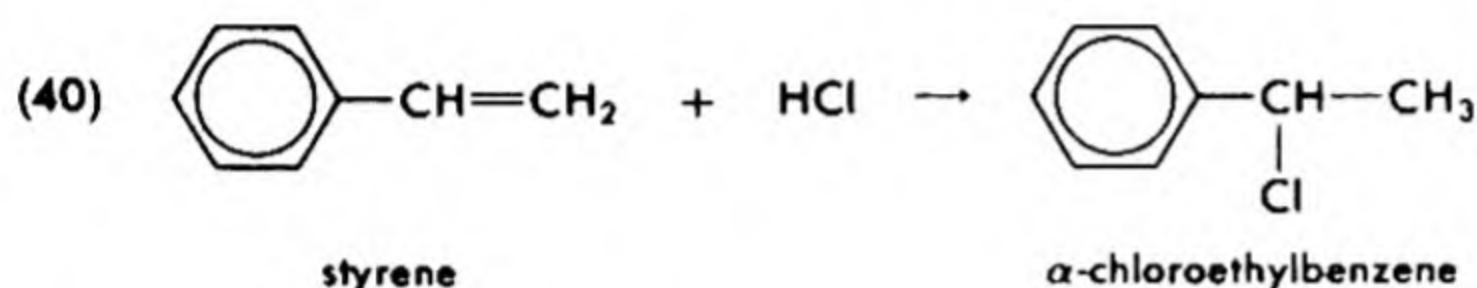
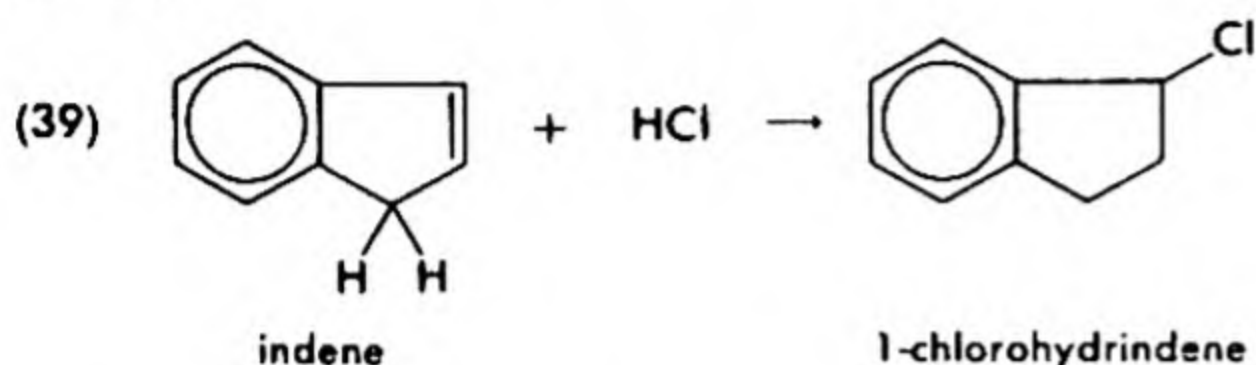


Halogens can be added stepwise to alkynes. To obtain halogens of different reactivity in the molecule, the second mole of halogen added can be different from the first. Some of these are probably free-radical reactions. One mole of iodine can be added to acetylene.



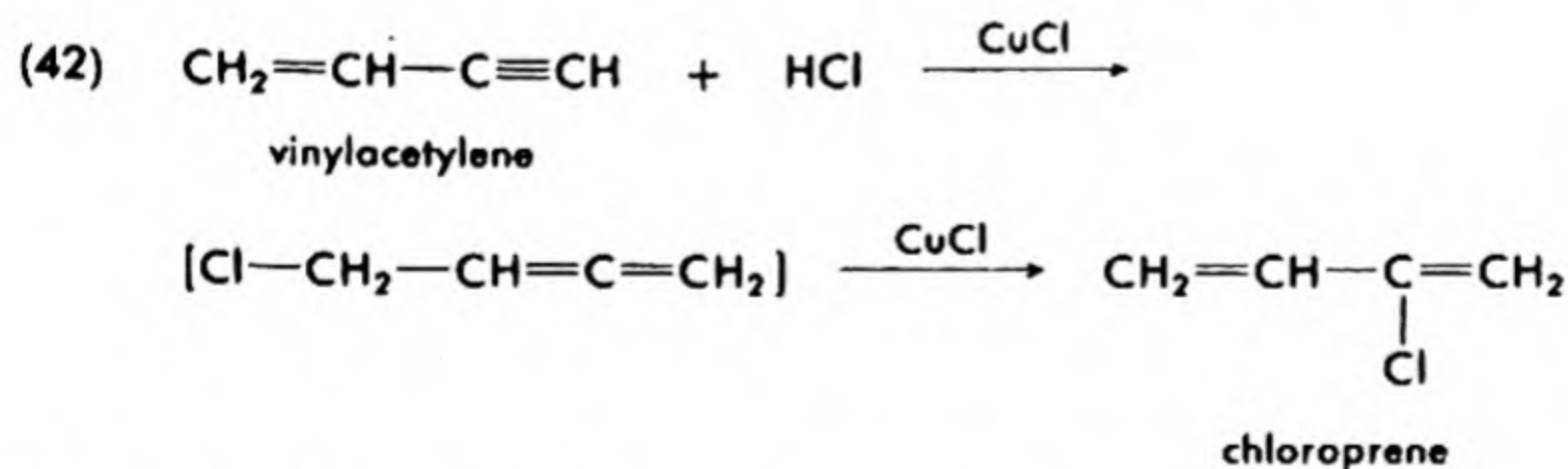
The ease of addition of halogen acids to olefins increases in the order chloride to bromide to iodide. Lewis acids are frequently used to catalyze

the addition of hydrogen chloride, although the following additions proceed simply by bubbling hydrogen chloride into the unsaturated starting materials. The examples, showing various directive effects, are the preparation of 1-chlorohydrindene, α -chloroethylbenzene, and β -chloropropionitrile.

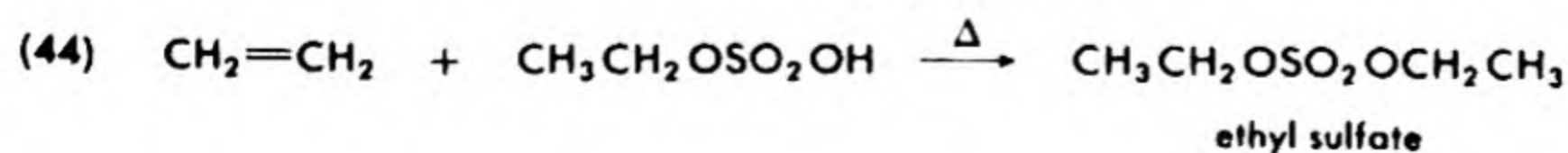
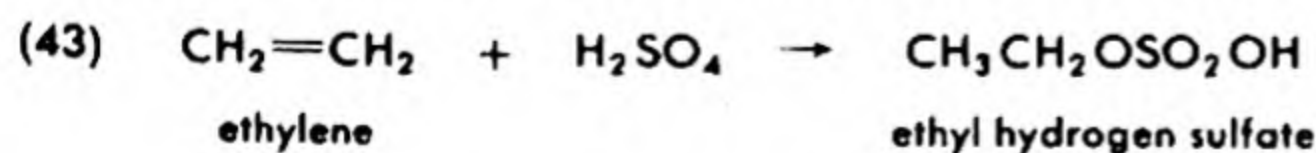


β -Bromopropionitrile is prepared by addition of hydrogen bromide to acrylonitrile in 88% yield.

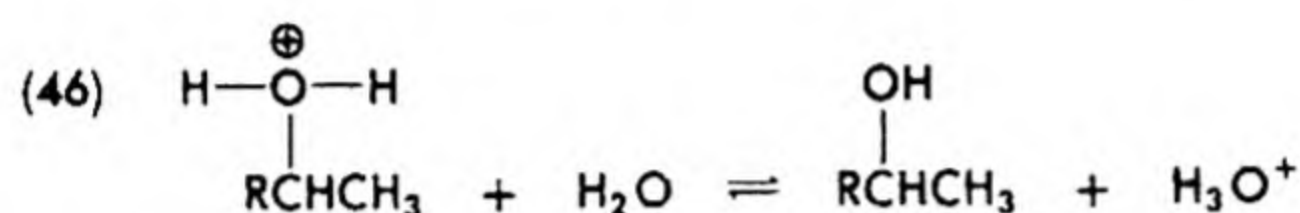
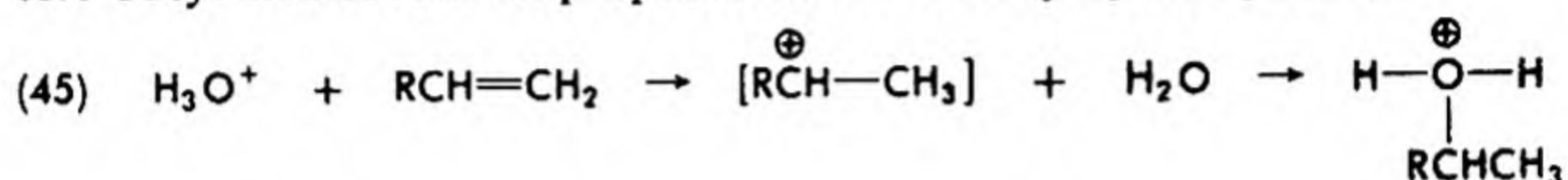
Addition of hydrogen chloride to vinylacetylene gives chloroprene, the raw material for neoprene rubbers. The intermediate chloromethylallene can be isolated, but undergoes a cuprous chloride catalyzed rearrangement via a carbonium ion to chloroprene (eq. 42).



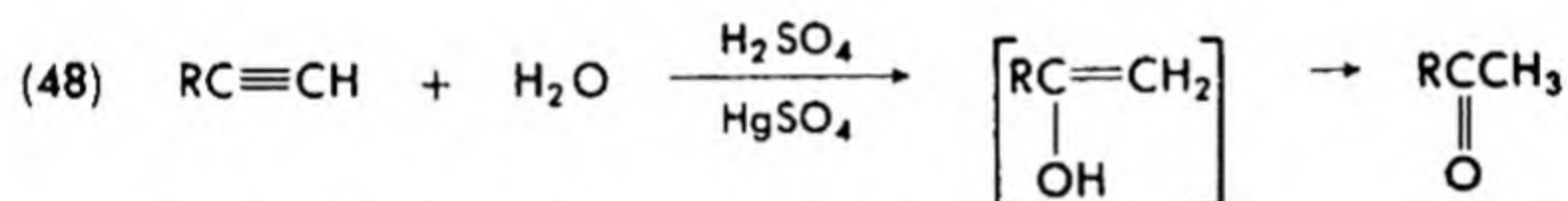
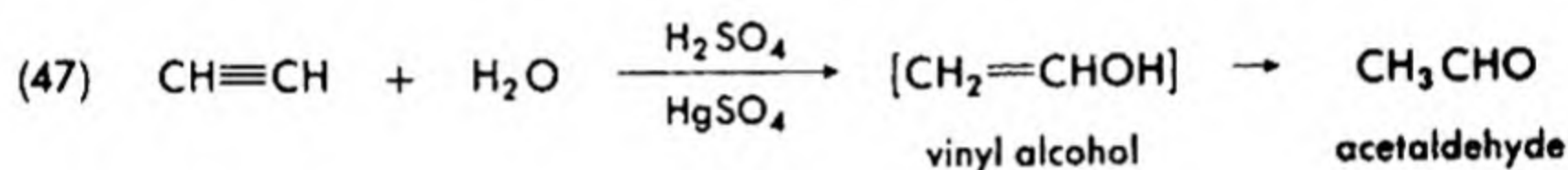
Sulfuric acid adds to olefins very readily. The solubility of alkenes and alkynes in concentrated sulfuric acid is due to formation of acid sulfates.



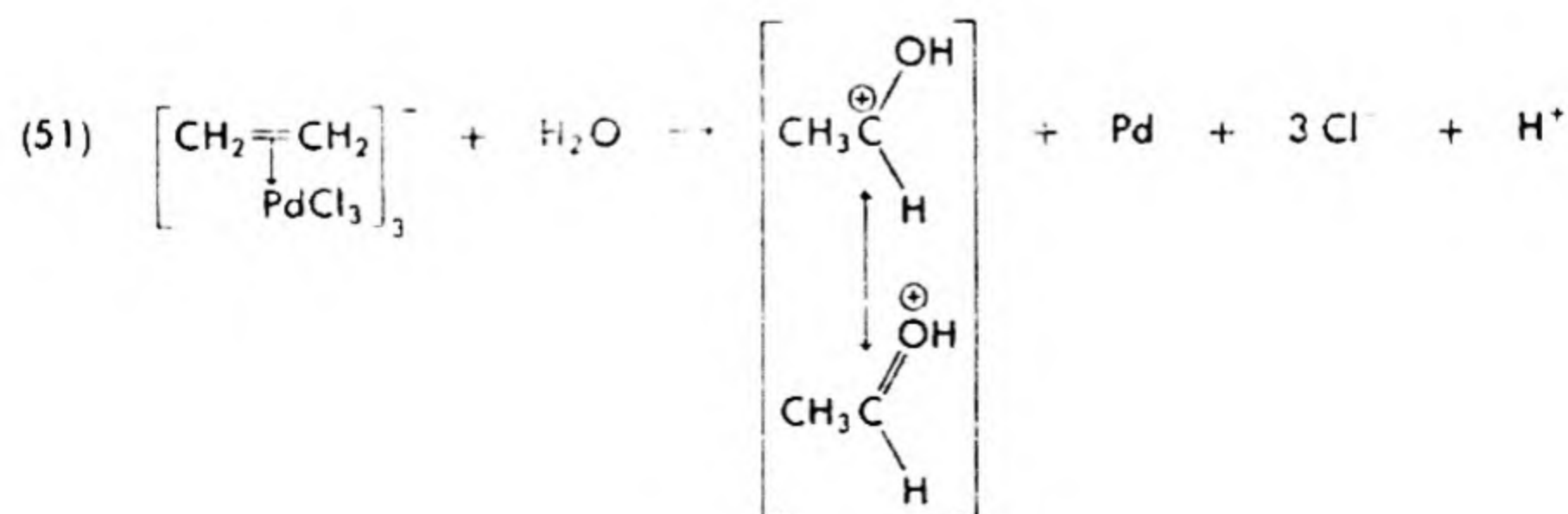
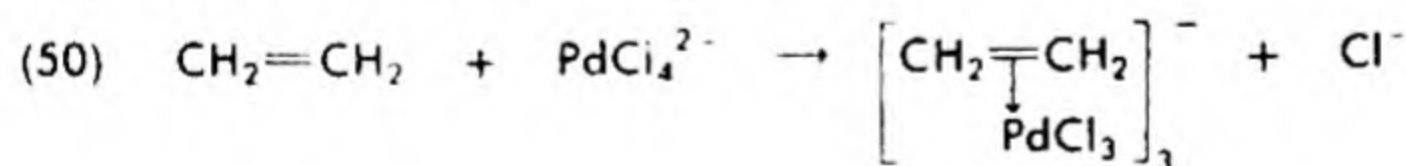
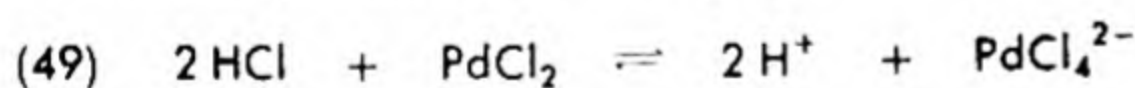
Hydration of alkenes to alcohols with dilute sulfuric acid has been considered to proceed through addition of the sulfuric acid to the olefin, followed by acid-catalyzed hydrolysis to the alcohol and sulfuric acid. This mechanism may play a minor role in hydration of olefins, but the more probable course of reaction is simply acid-catalyzed addition of water (eqs. 45 and 46). Ethanol, isopropyl alcohol, *sec*-butyl alcohol, and *tert*-butyl alcohol are all prepared commercially by this process.

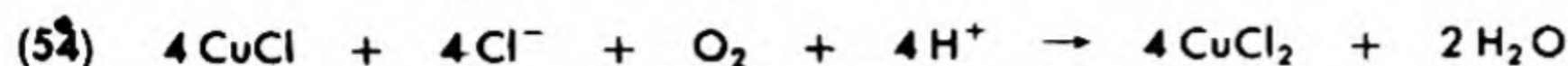
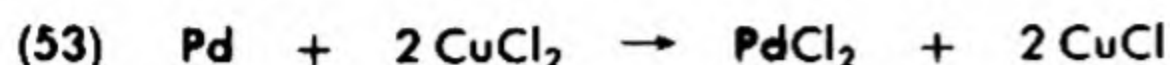
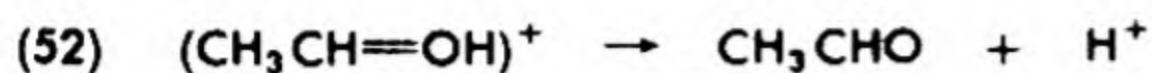


Addition of water to alkynes is an industrial method of preparing acetaldehyde and may also be used for the synthesis of ketones. The method is severely limited, however, by the availability of higher alkynes. In addition to sulfuric acid, mercuric sulfate is required as a catalyst.

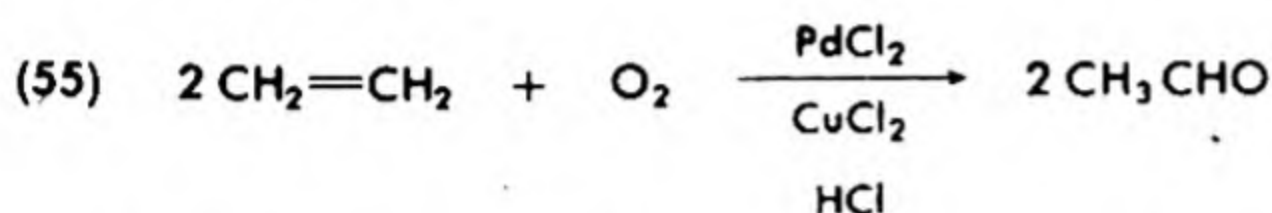


An industrial synthesis of acetaldehyde introduced in Europe in 1962 begins with ethylene, which is treated with aqueous palladium chloride, hydrogen chloride, cupric chloride, and air. This reaction involves a rearrangement and encompasses the following steps. (Eq. (51) represents several as yet undefined steps.)





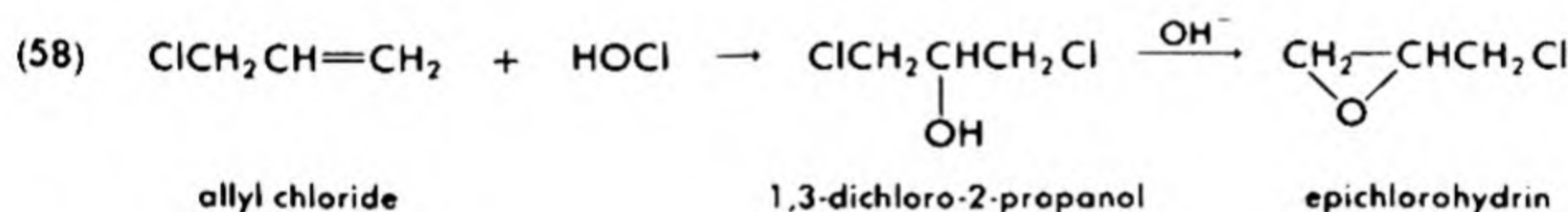
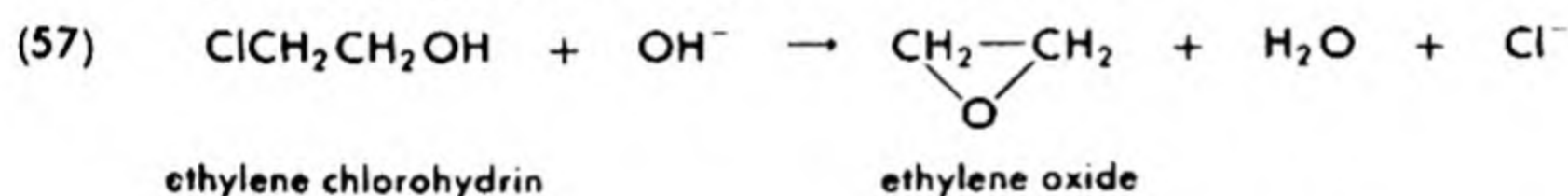
The overall reaction consumes only ethylene and oxygen, according to the stoichiometry.



Addition of hypochlorous acid to olefins gives vicinal chlorohydrins useful for the preparation of glycols and epoxy compounds. 1-Chloro-2-propanol is an example.



Ethylene oxide and epichlorohydrin are manufactured by way of the chlorohydrins (eqs. (57) and (58) and §13-4B).



E. Side Reactions

A prevalent side reaction occurring in additions to carbon-carbon multiple bonds is addition contrary to the expected mode. Although electronic interactions favor a specific product, there is inevitably a small degree of contrary addition due to participation of the less probable, but still possible, reactive intermediate. Usually this accounts for less than 10% of the total reaction, however. More serious is anti-Markovnikoff addition via another mechanism with certain specific reagents (e.g., HBr). Exclusion of free radical promoters (peroxides, light) avoids this.

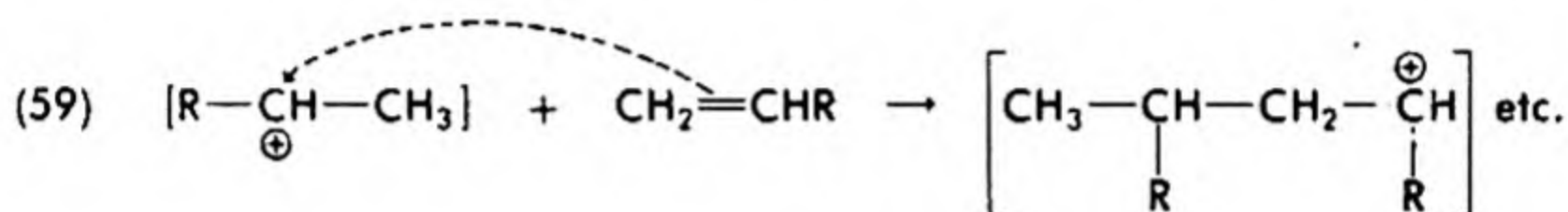
The distribution of 1,2-addition vs. 1,4-addition in conjugated systems involves similar multiplicity of active centers in a molecule. Sometimes the one predominates; sometimes, the other, but if both are possible, both occur to some extent.

In halogenation, higher temperatures tend to favor substitution over addition. Consequently, careful control of temperature is essential to

prevent free radical or ionic substitution from occurring in addition to or in place of addition (see §15-3).

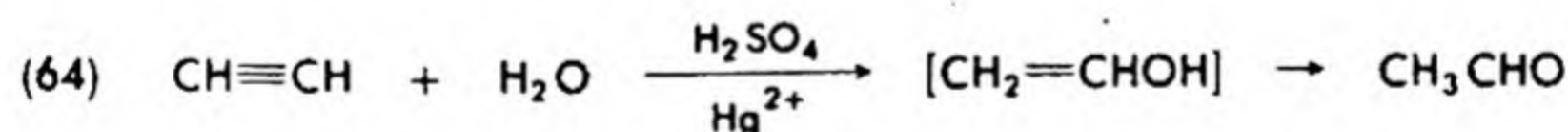
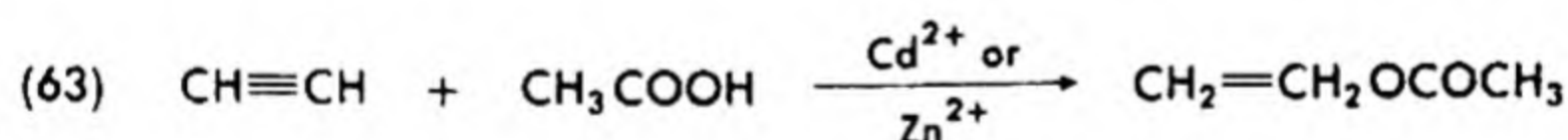
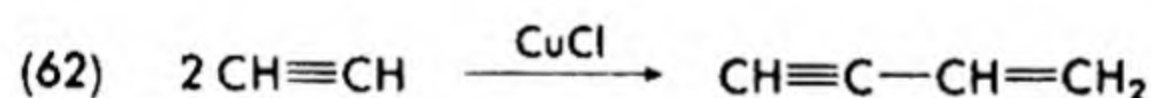
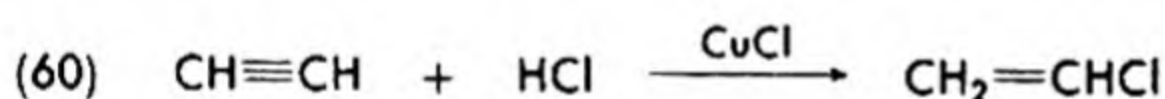
Stepwise addition to alkynes implicates side reactions involving more complete or less complete addition than desired. The former is more troublesome, since, as has been pointed out, the product with the double bond is sometimes more reactive than the original alkyne.

In many polar additions, the intermediate carbonium ion may attack an olefin molecule, resulting in dimerization or further polymerization.



14-3 ADDITIONS TO ACETYLENES. VINYLATION

Vinylation is a reaction in which an active hydrogen compound is added to acetylene to give a vinyl derivative. Certain of these have been industrially important for many years and are carried out at atmospheric pressure in the presence of acid catalysts or certain heavy metal salts. These include formation of vinyl chloride (eq. 60), acrylonitrile (eq. 61), vinylacetylene (eq. 62), vinyl acetate (eq. 63), and acetaldehyde (eq. 64).



The mechanisms of the heavy metal-catalyzed reactions of acetylenes are somewhat obscure and will not be discussed. Nucleophilic addition mechanisms will be treated in Chapter 17.

Vinyl compounds prepared from acetylene find considerable use as polymerization monomers. Although reactions with substituted acetylene are often similar to those with acetylene itself, these are not of industrial importance.

SUPPLEMENTARY READINGS

- Gould, E. S., *Mechanism and Structure in Organic Chemistry*, Holt-Dryden, New York, 1959, Chapter 13.
- Hine, J., *Physical Organic Chemistry*, 2nd Ed., McGraw-Hill, New York, 1962, Chapter 9.
- Ingold, C. K., *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N.Y., 1953, Chapter 12.

QUESTIONS AND PROBLEMS

1. Write equations for the reactions that occur when the following reagents are mixed. Include in the equations the structural formulas of those products formed in largest amount.

- | | |
|--|--|
| a. propylene + HBr with free radical inhibitor | e. benzoquinone + HBr |
| b. butadiene + Br ₂ (1 mole) | f. vinyl chloride + HOCl |
| c. allyl chloride + HOCl | g. isobutylene + H ₂ O + H ₂ SO ₄ |
| d. crotonaldehyde + HI | h. 2-pentene-4-yne + HCl (1 mole) |

2. State Markovnikoff's rule and explain it on the basis of electronic forces within the molecule.

3. Tell what is meant by 1,4-addition. Explain it on the basis of resonance in the reactive intermediates.

4. Show how the following compounds can be prepared in good yield from the suggested starting materials. Indicate necessary reagents, catalysts, and conditions. Use structural formulas for organic compounds.

- | | |
|--|--|
| a. 3-pentenoic acid from 1,3-butadiene | e. phenyl isopropyl ether from propylene and phenol |
| b. epoxyp propane from <i>n</i> -propyl alcohol | f. acetophenone from styrene |
| c. 2°-butyl alcohol from <i>n</i> -butyl alcohol | g. acetaldehyde from coke |
| d. 1,4-dibromo-2-butene from butadiene | h. ethyl β-methoxybutyrate from ethyl crotonate and methanol |
| | i. 1-bromo-2-butene from 2-bromobutane |

5. Write equations for the reactions that occur when the following reagents are mixed. Use structural formulas for organic compounds. Indicate essential special conditions.

- | | |
|---|---|
| a. 2-butyne and anhydrous hydrogen chloride | b. methylacetylene and hydrogen cyanide |
|---|---|

6. Show how the following compounds can be prepared from acetylene and inorganic reagents. Indicate necessary reagents, catalysts, and conditions. Use structural formulas for organic compounds.

- a. chloroprene
- b. lactic acid

- c. acrylic acid
- d. 1,1,2-trichloroethane

15

Halogenation and Addition by Free Radical Processes

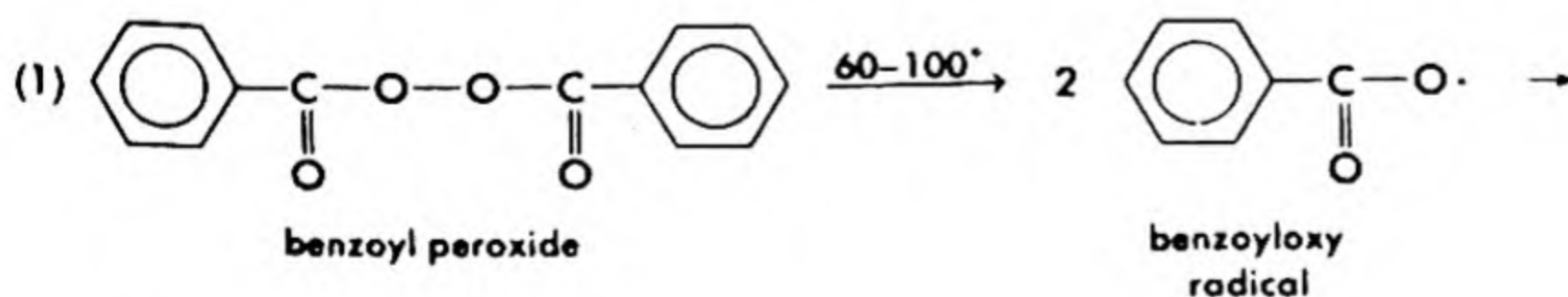
15-1 THE HOMOLYTIC, OR FREE RADICAL, PROCESS

We have discussed the two heterolytic, or "ionic" processes, attack by a nucleophilic reagent (Chapters 12 and 13) and attack by an electrophilic reagent (Chapter 14). It was noted that these reactions involved electron-pair donation to the substrate, and electron-pair acceptance from the substrate, respectively. A third process of interest to the organic chemist involves electron pairing-unpairing reactions, of which certain halogenation reactions form a relatively simple example. The species involved in such reactions which have atoms with one or more *unpaired* electrons are called *free radicals*, or sometimes *radicals* (terms now used interchangeably).

A. Characteristics of Free Radical Reactions

The evidence for free radicals and their properties are discussed more fully in Chapter 26. The present discussion is limited to a delineation of those characteristics of free radical halogenation which most typically distinguish this type of reaction from the electrophilic reactions of halogens.

The reaction of methane with chlorine is typical. This reaction occurs effectively in the gas phase (whereas electrophilic addition of bromine to olefins is favored by the presence of Lewis acids in liquid solution). It is not promoted by acidic or basic catalysts, but is promoted by light or the presence of organic peroxides, such as benzoyl peroxide, which are known



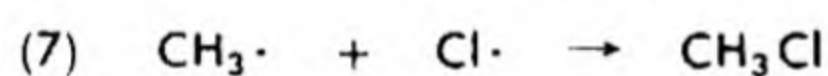
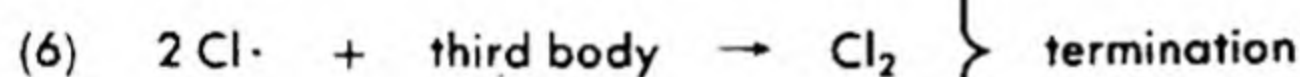
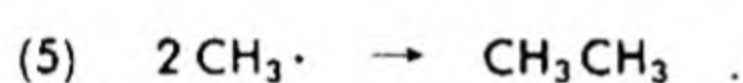
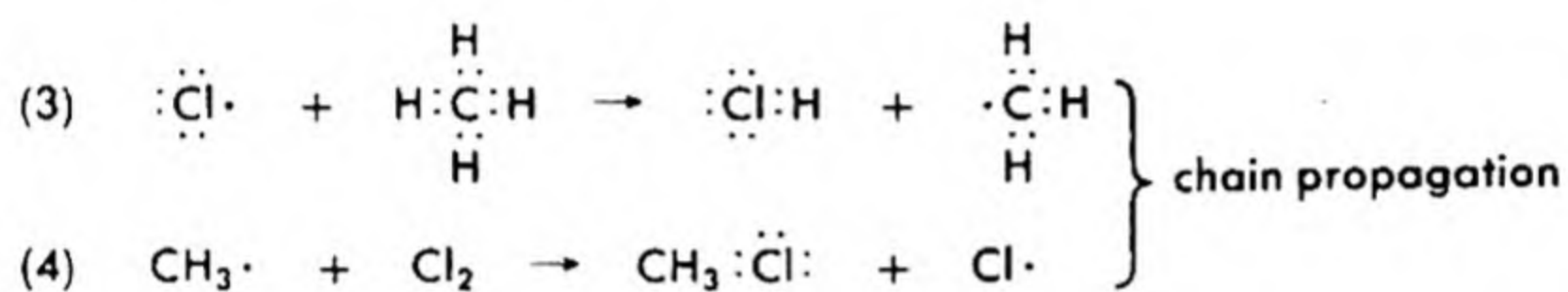
phenyl
radical

to decompose thermally to provide free radicals. The peroxides, called *initiators*, are consumed in the reaction, but many moles of product are obtained per mole of initiator used.

This and other evidence have led to the concept of the *chain reaction*, in which a reactive species, once formed, provides a new reactive species in each subsequent step of the reaction.

15-2 CHLORINATION OF METHANE, A TYPICAL FREE RADICAL CHAIN REACTION

Studies of the reaction between methane and chlorine to give methyl chloride and hydrogen chloride have shown that it probably occurs in the manner indicated by eqs. (2) to (7).



} termination

Initiation of the reaction occurs by light absorption (eq. 2). Each chlorine atom produced can now react with a methane molecule by a radical displacement reaction on hydrogen to give a molecule of hydrogen chloride and displace a methyl radical (eq. 3). The methyl radical, in turn, reacts with a chlorine molecule to give a molecule of methyl chloride and a chlorine atom (eq. 4). Once such a system is started, it is self-perpetuating in principle and could continue by a repetition of (3) and (4) until all of the chlorine or methane is exhausted. Such a process is called a chain reaction, since it occurs by repeated links interlocked with each other by the reforming of the necessary reactive intermediates. The chlorine atom consumed in (3) is replaced in (4) and the methyl radical consumed in (4) is replaced in (3). The chains are not endless, however, because they are terminated when two radicals combine (eq. 5-7). New chains continue to be initiated by photolysis of chlorine, at constant temperature, so that a steady state situation is soon achieved in which initiation and termination reactions occur at equal rates. The average number of molecules of methyl chloride produced per quantum of light absorbed is called the *quantum yield*. The value of the quantum yield depends upon the condi-

tions of the experiment and is a function of the rates of the chain propagation vs. termination reactions; values as high as 1000 are not uncommon.

Further chlorination of the methyl chloride and the resulting higher chloromethanes occurs by the same kind of free radical attack by chlorine atoms.

Since chlorine atoms can also be produced thermally at convenient rates by heating chlorine molecules to temperatures above 300°, the free radical chlorination of methane or of other aliphatic hydrocarbons can be conducted in the dark at these temperatures. One often uses initiators which decompose thermally at lower temperatures, such as benzoyl peroxide (eq. 1), to initiate chains by the steps indicated by eqs. (8) and (9). This permits chlorinations to be conducted readily at temperatures below 100° and in the absence of electromagnetic radiation. When the rate of



a reaction is increased substantially by a free radical initiator, this is *prima facie* evidence that a free radical chain is involved.

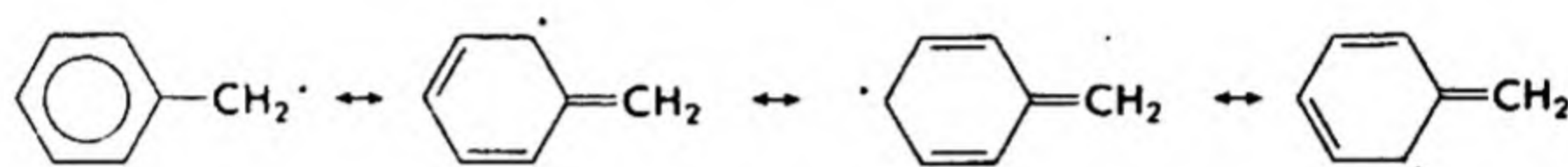
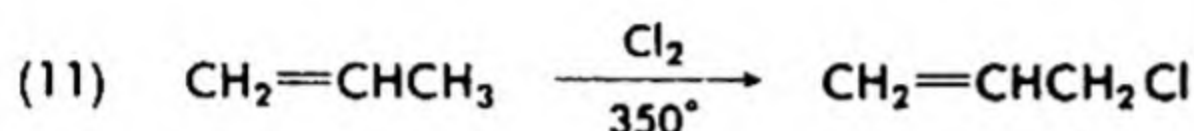
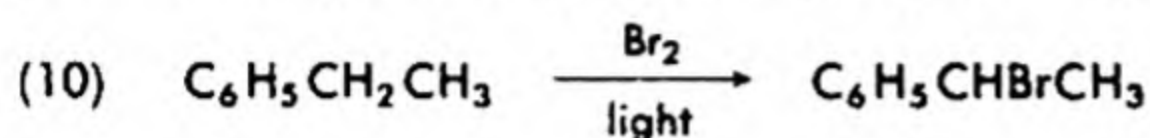
15-3 POSITIONAL SELECTIVITY OF RADICAL REACTIONS

Free radicals are formed in homolysis most readily when they are stable. One might anticipate a similar effect in radical displacement reactions. Such is the case; therefore, chlorine atoms and other free radicals show some selectivity in the hydrogens they attack even in completely paraffinic systems. Thus, at 300° in the vapor phase, tertiary hydrogens are attacked by chlorine atoms about five times as rapidly as primary, and secondary hydrogens about three times as rapidly as primary. At lower temperatures, the selectivity is greater and it is greater still with less reactive radicals such as bromine atoms (Table 15-1).

TABLE 15-1. Relative Reactivities of Primary, Secondary, and Tertiary Hydrogen Atoms to Free Radical Displacements in Alkanes

Reagent	Relative Reactivity of:	
	2° H	3° H
Cl ₂ , 300°, gas phase	3.3 × 1°	4.4 × 1°
Cl ₂ , 100°, gas phase	4.3 × 1°	7.0 × 1°
Cl ₂ , 100°, CCl ₄ solution	2.0 × 1°	3.0 × 1°
Cl ₂ , 0°, CCl ₄ solution	4.5 × 1°	7.0 × 1°
Br ₂ , 60°, gas phase	(1° insignificant)	30-50 × 2°

The difference in reactivity is associated, at least in part, with the greater stability of tertiary radicals over secondary and primary. Such reactivity differences caused by stabilizations in the transition states for radical displacements are reflected in the fact that bromination of ethylbenzene leads almost exclusively to α -phenylethyl bromide (eq. 10) and that higher temperature chlorination of propylene gives allyl chloride (eq. 11). Such reactions proceed through the resonance-stabilized α -phenylethyl radical (similar to I) and allyl radical, respectively.



benzyl radical valence-bond structures



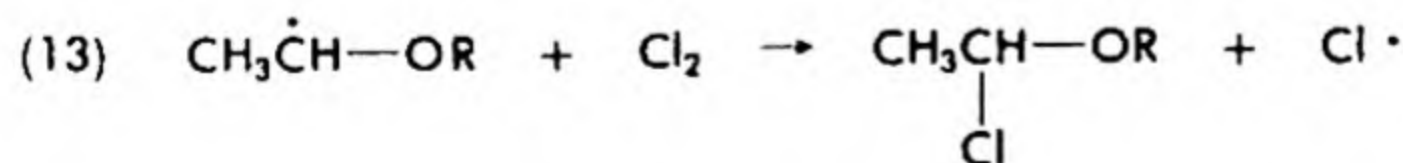
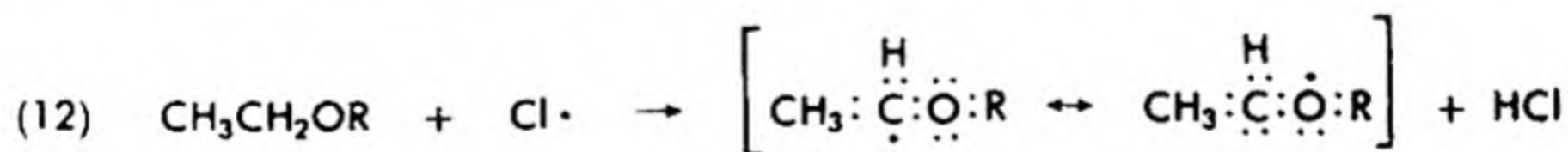
allyl radical valence-bond structures



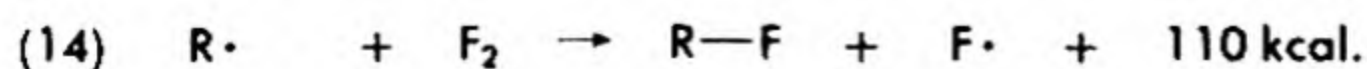
allyl radical resonance hybrid

It may be noted that the molecular orbitals for these systems are the same as those of the analogous carbonium ions (see Figs. 12-9 and 12-10) but contain one more electron in each system.

Other groups that can conjugate with the odd electron also activate α -positions. Thus, ethers react with chlorine atoms to give resonance-stabilized radicals (eq. 12) that lead to α -chloroethers (eq. 13).

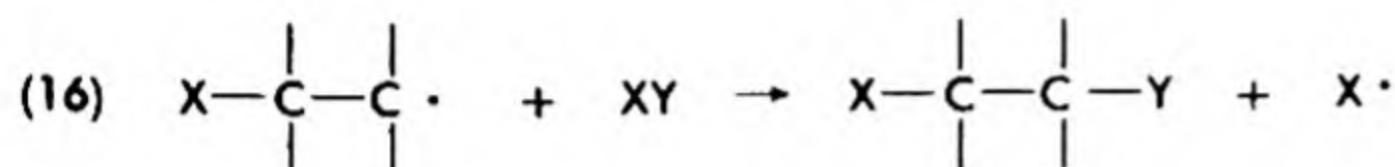
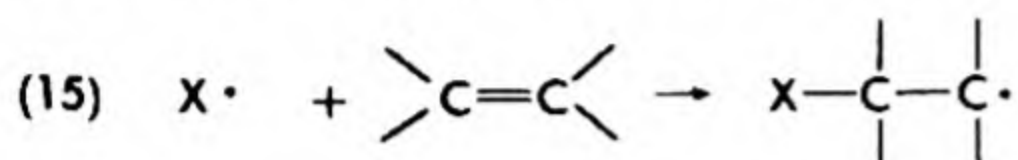


Fluorine is not only nonselective, but highly fragmenting in its reactions with alkanes. This can be expected from the highly exothermic character of the reaction (eq. 14) which provides ample energy for C—C bond cleavage (≈ 90 kcal./mole).

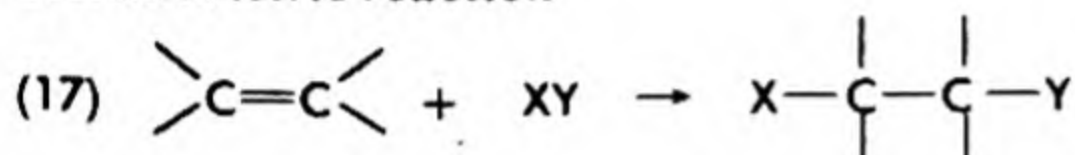


15.4 ADDITION TO CARBON-CARBON DOUBLE BONDS

Free radicals can, as described above, pair their electrons by radical displacement or by coordination with another radical. Another reaction which provides for electron pairing involves addition to a multiple bond. As this reaction leads to a new radical, this can be one step in a chain. The generalized chain for such addition reactions is given in eqs. (15) and (16) and the overall reaction in eq. (17).



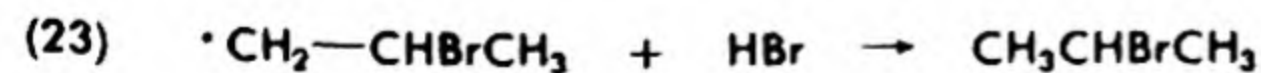
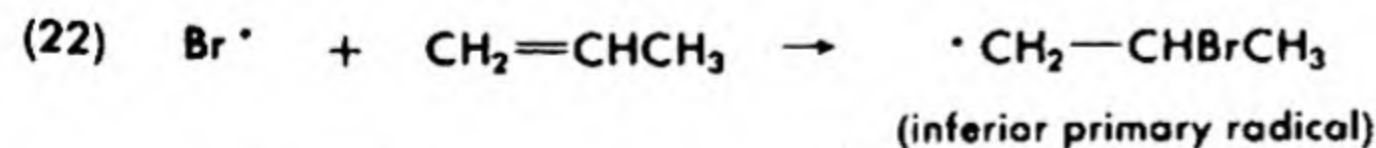
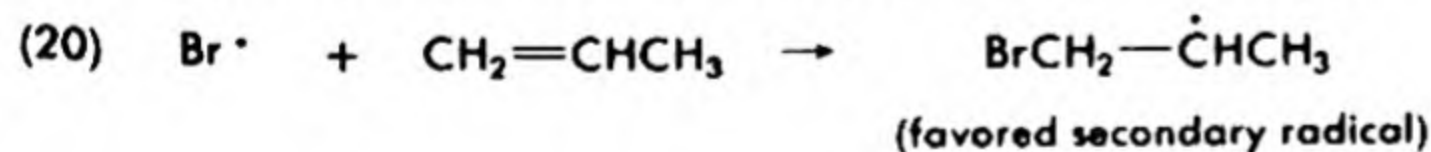
Stoichiometric reaction



Since many olefins add chlorine or bromine very sluggishly in the dark, light or radical initiators are often used to promote reaction. For example, addition of chlorine to tetrachloroethylene (eq. 18) and the addition of bromine to cinnamic acid (eq. 19) are light-promoted chain reactions. In some cases, even iodine can be added photochemically.



Hydrogen bromide generally gives different products when added to olefins under radical conditions (anti-Markovnikov addition) as compared with those obtained under ionic (heterolytic) conditions, §14.2B. After the radicals are formed by an initiation process, the chain steps in addition to propylene could be (20) and (21) or (22) and (23). Step 20 is faster than



(22) to form a secondary radical rather than a primary one; thus, *n*-propyl bromide is obtained rather than isopropyl bromide.

Ethyl bromide is now made industrially by the addition of hydrogen bromide to ethylene using radioactive materials to initiate the chains.

15.5 ENERGY REQUIREMENTS OF FREE RADICAL CHAINS

Fast free radical chains are possible only when both steps in the chain have very low free energies of activation. Activation energies of reactions can be low only if the reactions are exergonic, since a molecule must acquire at least the energy of reaction in order to react. This makes the selection of addends for free radical addition quite narrow and to some extent rather different for different types of olefinic compounds. In the absence of data on entropies of reaction, ΔH can be used as a rough approximation for ΔF . Thus, of the compounds listed in Table 15-2, only HBr, H_2S , HOCl, Cl_2 , and Br_2 have the required negative heats of reaction for both the radical + ethylene reaction and the alkyl radical + inorganic molecule reaction. Thus, HBr can readily be made to add contrary to Markovnikoff's rule simply by the introduction of a radical source such as a peroxide or oxygen, if the ionic reaction is not too fast.

TABLE 15-2. Heats of Reaction of Free Radical Addition Chain Steps (Ethylene), kcal./mole at 25°C

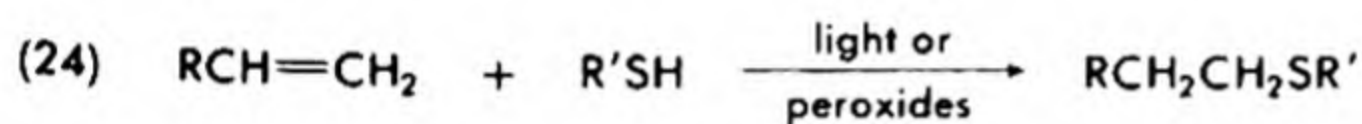
Y—Z	ΔH $\text{Z} \cdot + \text{CH}_2=\text{CH}_2$	ΔH $\text{Z}-\text{CH}_2-\text{CH}_2 \cdot + \text{Y}-\text{Z}$
H—NH ₂	-17	+ 4
H—OH	-32	+22
H—SH	-16	- 8
H—Cl	-26	+ 5
H—Br	- 5	-11
H—I	+ 7	-27
Cl—Cl	-26	-19
Br—Br	- 5	-17
I—I	+ 7	-13
Cl—OH	-32	-17

From Table 15-3 it appears that some of the compounds that add readily to ethylene by free radical chains may add less readily to styrene. The heats of reaction for addition of radicals to styrene (Table 15-3) are considerably more exothermic than comparable additions to ethylene, whereas reactions of the phenylethyl radicals are more endothermic or less exothermic than comparable reactions of ethyl radicals. Both factors are due to resonance stabilization of the α -phenylethyl free radicals, similar to formula I.

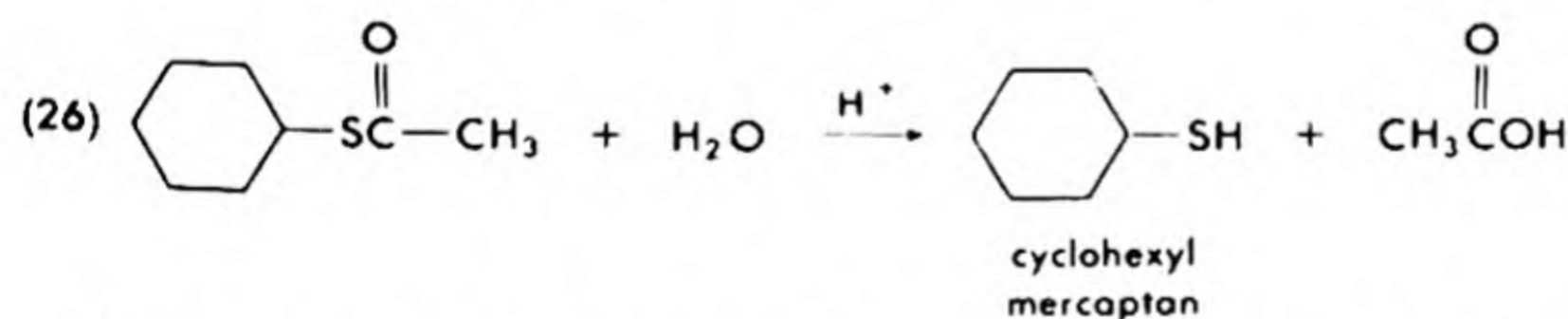
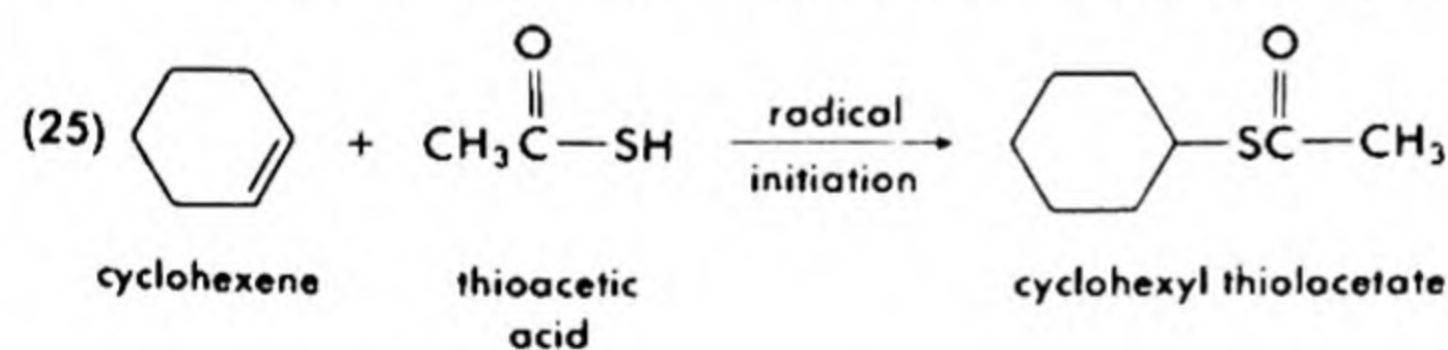
TABLE 15-3. Heats of Reaction of Free Radical Addition Chain Steps (Styrene), kcal./mole at 25°C

Y—Z	ΔH $Z\cdot + \text{CH}_2=\text{CH}-\text{C}_6\text{H}_5$	ΔH $Z-\text{CH}_2-\dot{\text{C}}\text{H}-\text{C}_6\text{H}_5 + \text{Y}-\text{Z}$
H—SH	-39	+16.5
H—Cl	-49	+26
H—Br	-28	+13.5
H—I	-16	-3.5
Cl—Cl	-49	-6
Br—Br	-28	0
I—I	-16	+1

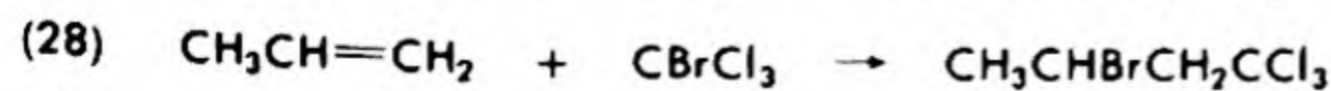
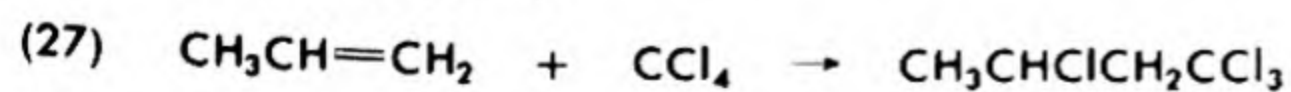
Of the hydrogen halides, only hydrogen bromide gives long-chain radical processes readily with alkenes. Hydrogen iodide does not add readily under radical conditions as the step analogous to (20) has its equilibrium to the left, and hydrogen chloride has a very slow step analogous to (21). Mercaptans do react readily, however, to give thioethers by radical chains (eq. 24).



The addition of thioacetic acid to olefins (eq. 25) followed by hydrolysis of the thioesters (eq. 26) is an excellent mercaptan synthesis.

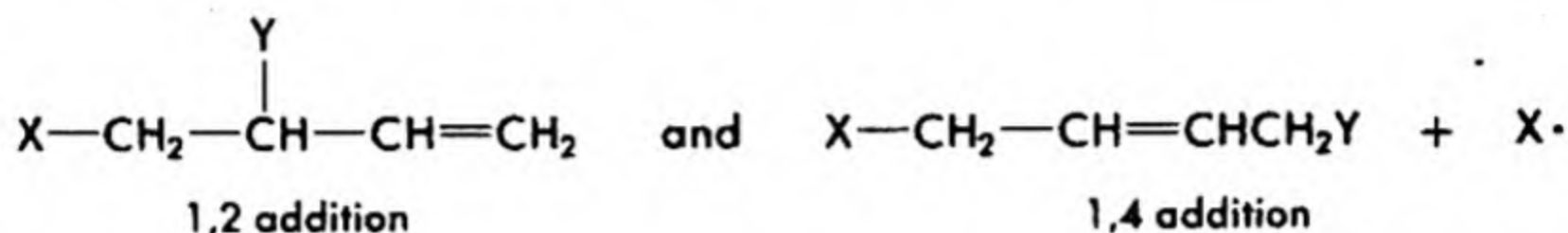
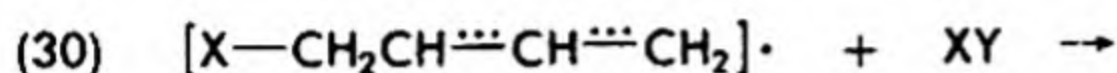
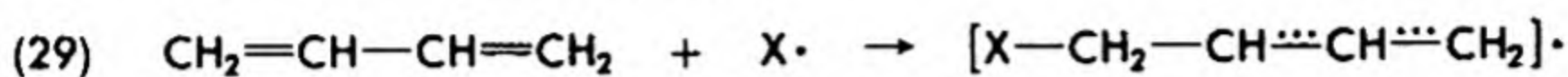


Certain polyhalomethanes add readily to olefins by the free radical mechanism. Among these are carbon tetrachloride (eq. 27) and bromotrchloromethane (eq. 28). In these reactions, a halogen atom is abstracted by an alkyl radical (eq. 16). The remaining trichloromethyl radical is the chain carrier (eq. 15).

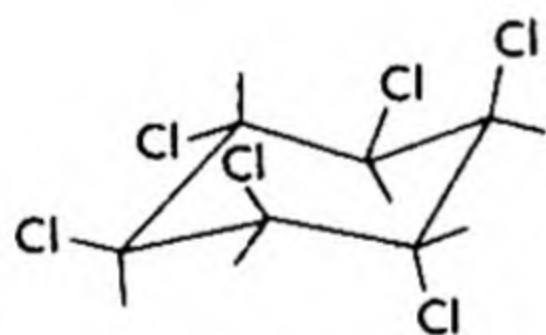
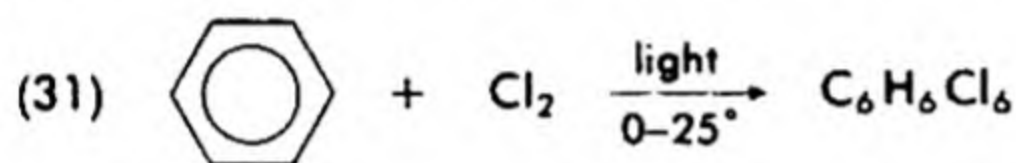


15-6 CONJUGATE FREE RADICAL ADDITION

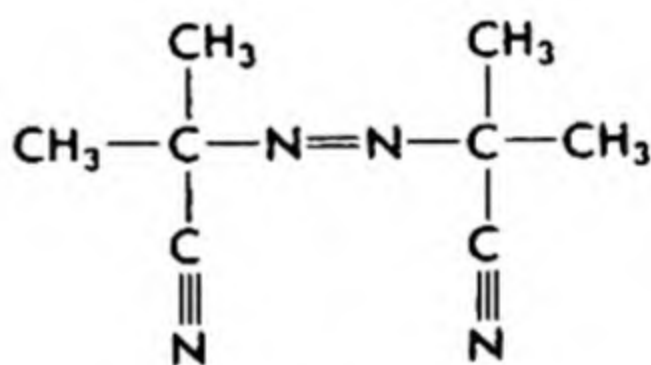
In a conjugated diene, addition of a radical gives an allylic radical (eq. 29). As is the case for allylic carbonium ions, resonance divides the radical activity between the two allylic positions to result in 1,2- or 1,4-addition products (outline 30).



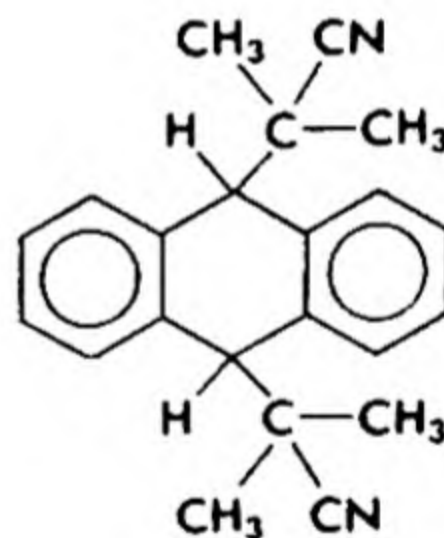
Radicals can add to aromatic systems. Even benzene adds chlorine atoms to give a mixture of stereoisomeric 1,2,3,4,5,6-hexachlorocyclohexanes (eq. 31). About 15% of this mixture is the γ isomer, which is a potent insecticide called lindane.



lindane



azoisobutyronitrile



II

Aromatic systems such as anthracene, which can be attacked with smaller loss of resonance energy, add even more stable radicals; thus anthracene reacts with the fairly stable cyanoisopropyl radicals from azoisobutyronitrile to give an addition product, II.

SUPPLEMENTARY READINGS

- Bohm, B. A., and P. I. Abell, "Stereochemistry of Free Radical Additions to Olefins," *Chem Rev.* **62**, 599-609, 1962.
- Chiltz, G., P. Goldfinger, G. Huybrechts, G. Martens, and G. Verbeke, "Atomic Chlorination of Simple Hydrocarbon Derivatives in the Gas Phase," *Chem. Rev.* **63**, 355-372 (1962).
- Goldwhite, M., "The Side-Chain Halogenation of *n*-Alkyl Benzenes," *J. Chem. Educ.* **37**, 295-296 (1960).

Knox, B. E., and H. G. Palmer, "Bond Dissociation Energies in Small Hydrocarbon Molecules," *Chem Rev.* **61**, 247-255 (1961).
 Walling, C., *Free Radicals in Solution*, Wiley, New York, 1957, Chapters 7 and 8.

QUESTIONS AND PROBLEMS

1. Evaluate the conclusions of the author in Supplementary Reading 3 in the light of the evidence he presents. What are some of the factors which may operate to complicate the simple assertions of §15-3 regarding halogenation in alkylarenes? Which of these might receive support from the data cited by Dr. Goldwhite?

2. Illustrate the following concepts by formulas or equations involving real compounds other than methane.

- | | |
|---------------------|-------------------------|
| a. free radical | d. chain propagation |
| b. chain reaction | e. chain termination |
| c. chain initiation | f. heterolytic reaction |

3. Write equations for the reactions that occur to form the majority of products from the following mixtures of reagents.

- | | |
|--|--|
| a. 1,3-pentadiene and hydrogen bromide with peroxide | d. 2-butene and chlorine, 0° |
| b. 1,3-pentadiene and hydrogen bromide in the dark with free radical inhibitor | e. <i>n</i> -propyl ether and bromine |
| c. 2-butene and chlorine, 350° | f. benzaldehyde and chlorine in sunlight |
| | g. propane and bromine |
| | h. isopentane and bromine |

4. Show how the following syntheses can be accomplished in satisfactory yield. Use structural formulas for organic compounds. Indicate necessary inorganic reagents and special conditions.

- | | |
|--|--|
| a. butanenitrile from propylene | f. 2-phenylethyl mercaptan from styrene |
| b. benzylamine from toluene | g. α, α' - <i>p</i> -xylylene diisocyanate from <i>p</i> -xylene |
| c. cyclohexanol from cyclohexane | h. isoamyl alcohol from neopentane |
| d. allyl nitrite from propylene | |
| e. 1-phenylethyl sulfide from ethylbenzene | |

5. A sample of 0.50 mole of isopentane was treated with 0.51 mole of chlorine at 100° in the gas phase.

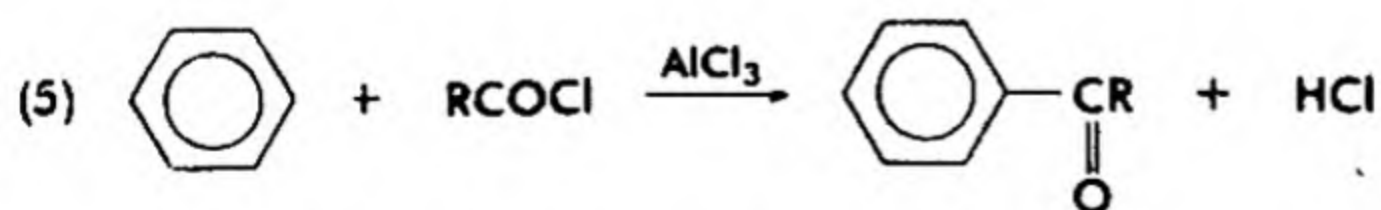
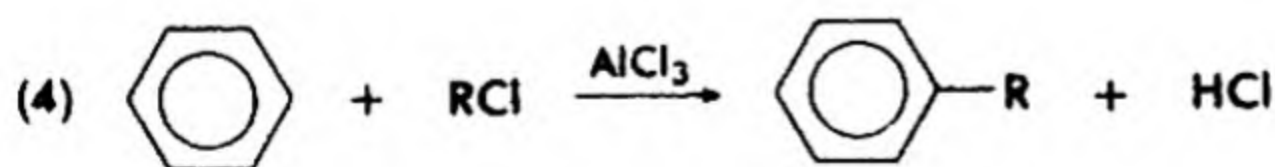
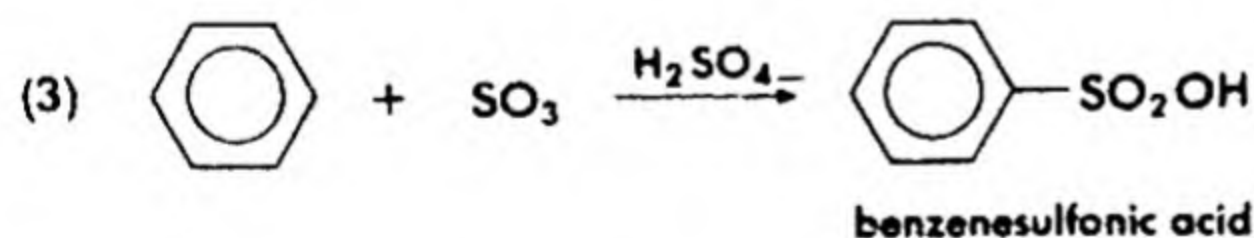
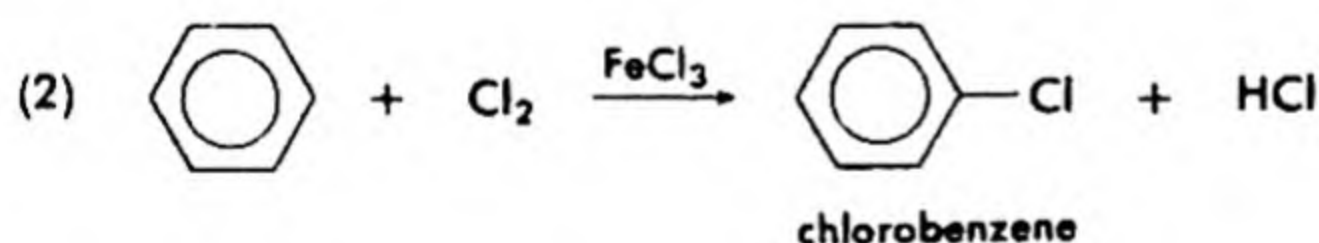
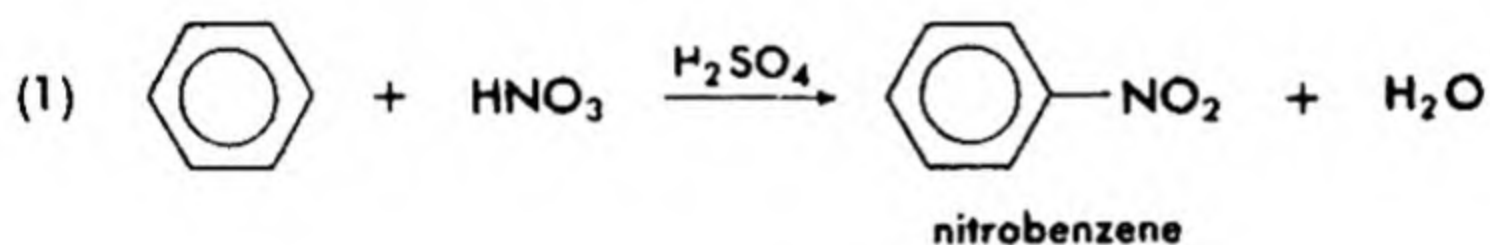
- Write structural formulas for all possible monosubstitution products.
- What other side reactions occur?
- Calculate the ratio in which the products indicated in (a) would be formed.
- If the chlorination were done at 300°, what would be the major product?
- Compare the yields of this product under both sets of conditions, assuming an equal amount of other side reactions.

16

Electrophilic Aromatic Substitution

16-1 NATURE OF ELECTROPHILIC AROMATIC SUBSTITUTION

The reactions which are to be considered in this chapter include, among others, aromatic nitration (eq. 1), halogenation (eq. 2), sulfonation (eq. 3), and Friedel-Crafts reactions (eqs. 4 and 5), all of which have important industrial and laboratory applications. These reactions involve attack on the benzene ring by an *electrophilic reagent*, which accepts an electron pair from the aromatic ring; thus, the latter acts as a nucleophile. Displacements on aromatic rings by nucleophiles, in which the ring acts as an electron acceptor, are discussed in Chapter 22.



It appears likely that many, and perhaps all, electrophilic aromatic substitutions involve the rate-determining formation of an intermediate

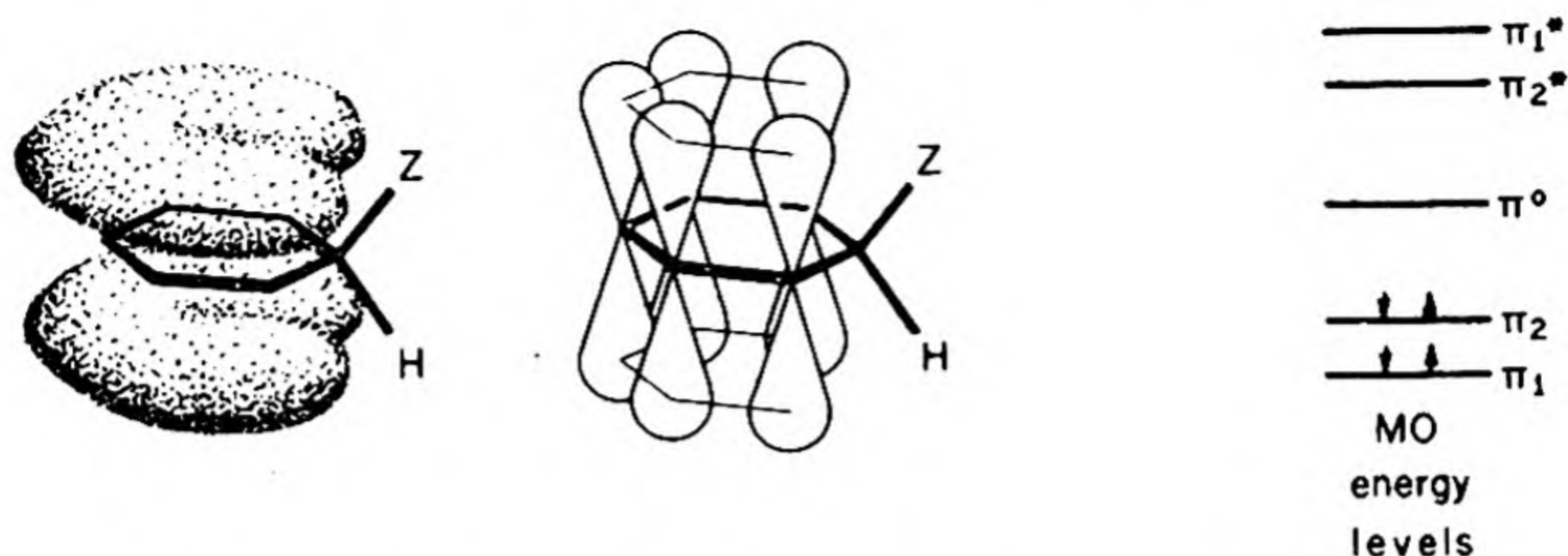
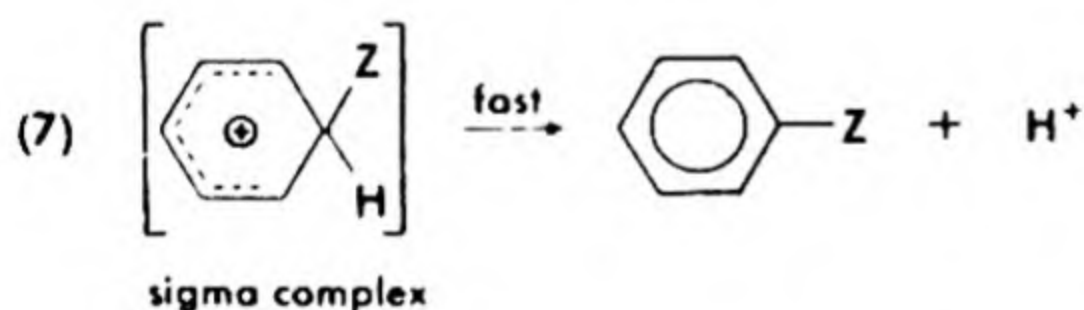
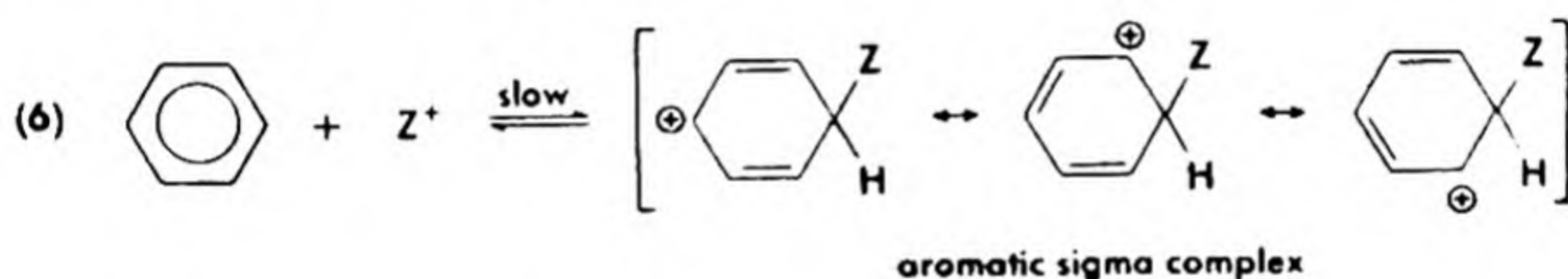


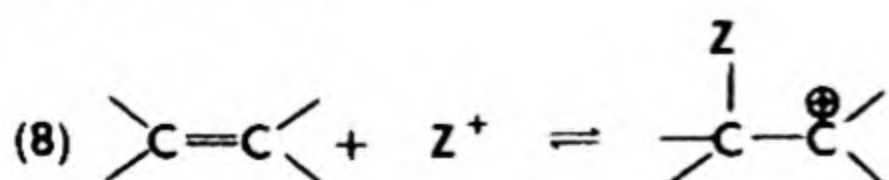
Fig. 16-1. MO Cloud and MO Formula for Low-Energy π Orbital of Electrophilic Aromatic Substitution Intermediate (Sigma Complex). Since this is a four-electron system, one more orbital is required.

sigma complex, Fig. 16-1, which rapidly loses a hydrogen ion to a proton acceptor in the environment to give a substituted aromatic compound. Indeed, a number of sigma complexes have recently been isolated under special conditions. The generalized mechanism, using Z^+ as an electrophile, is shown in eqs. (6) and (7).

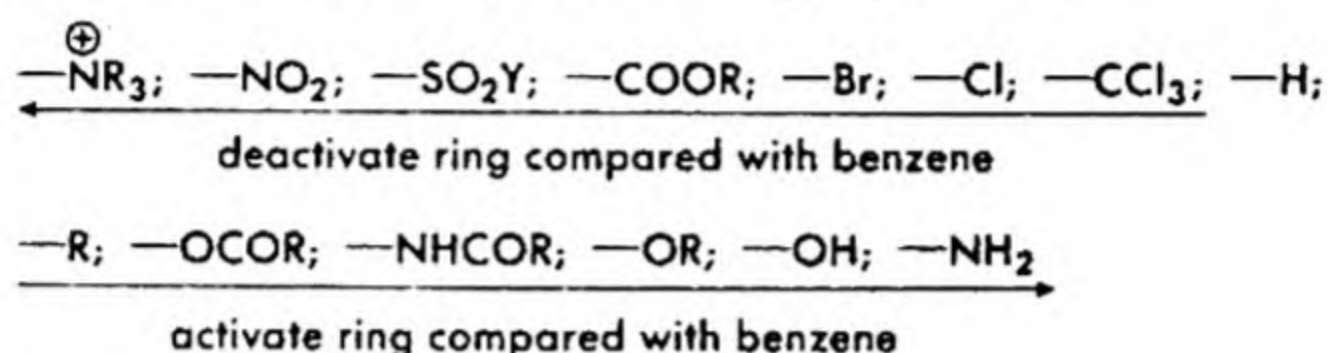


16-2 CORRELATION OF STRUCTURE WITH REACTIVITY IN AROMATIC COMPOUNDS

Since the aromatic compound acts as an electron-pair donor in these reactions, we should expect to find a structural correlation between reactivity in aromatic substitution reactions and reactivity in addition to olefins (Chapter 13), where the rate-determining step (eq. 8) represents the reaction between an electrophile, say Z^+ , and the olefin acting as a nucleophile.



In each case, one can anticipate that electron-releasing substituents should increase reactivity, as such substituents can stabilize the electron-deficient intermediate (and therefore the transition state leading to it). Electron-withdrawing substituents destabilize the intermediate and the corresponding transition state and thus decrease reactivity. The abilities of groups to withdraw or donate electrons are discussed in §10-2. A few groups arranged in increasing order of ring activation are listed as follows (the effect is discussed in length in §16-4 through §16-4C).

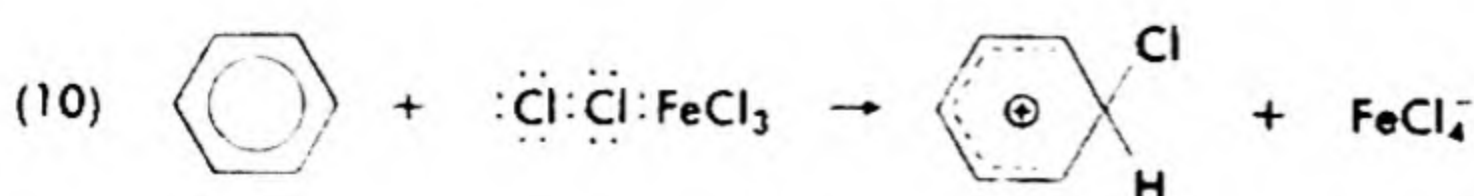
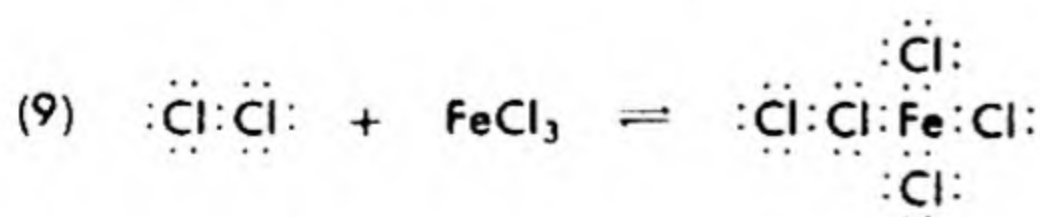


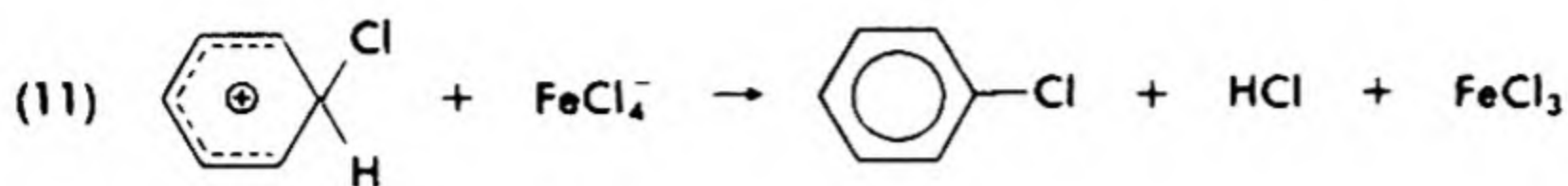
Activating substituents make possible the use of weaker reagents or lower temperatures, while deactivating groups increase the severity of conditions required. When rates of reaction depend on the aromatic compound, substituent effects are readily correlated with reactivities. In certain cases, rates are independent of the concentration and nature of the aromatic substrate. This occurs whenever steps *before* sigma complex formation become rate-determining. In such cases one can measure relative reactivities by competition experiments. Two aromatic substrates are placed together in a reaction mixture with the reagent to determine the relative extent of substitution on the two compounds.

16-3 ELECTROPHILIC REAGENTS

A. Reagents for Halogenation

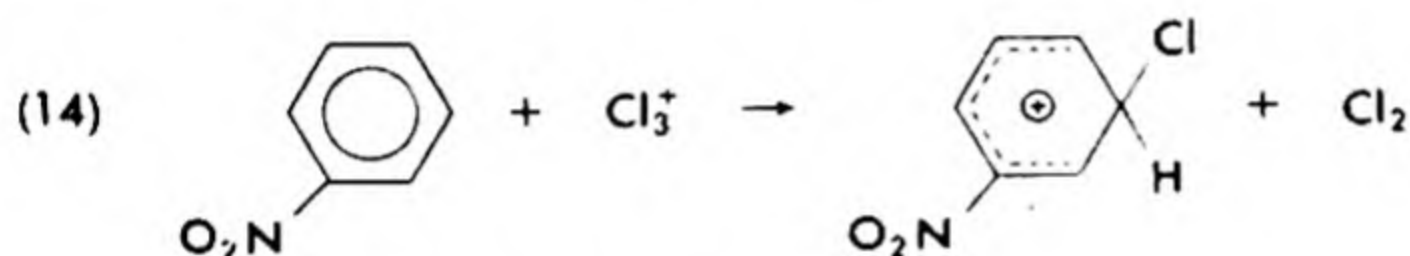
Benzene and other simple aromatic hydrocarbons do not react with chlorine or bromine in the dark at reasonable rates in the absence of a catalyst, but react readily (eq. 2) in the presence of strong Lewis acids, such as aluminum chloride, ferric chloride, or zinc chloride. The reactions are often promoted by the addition of iron filings or nails, which in the presence of chlorine or bromine give the corresponding ferric halide. The Lewis acid coordinates with the halogen (eq. 9) so that the nucleophilic displacement on halogen (eq. 10) is rendered less difficult by the extra stabilization of the halide ion—Lewis acid bond strength. The reaction is completed by a relatively fast proton transfer reaction (eq. 11).





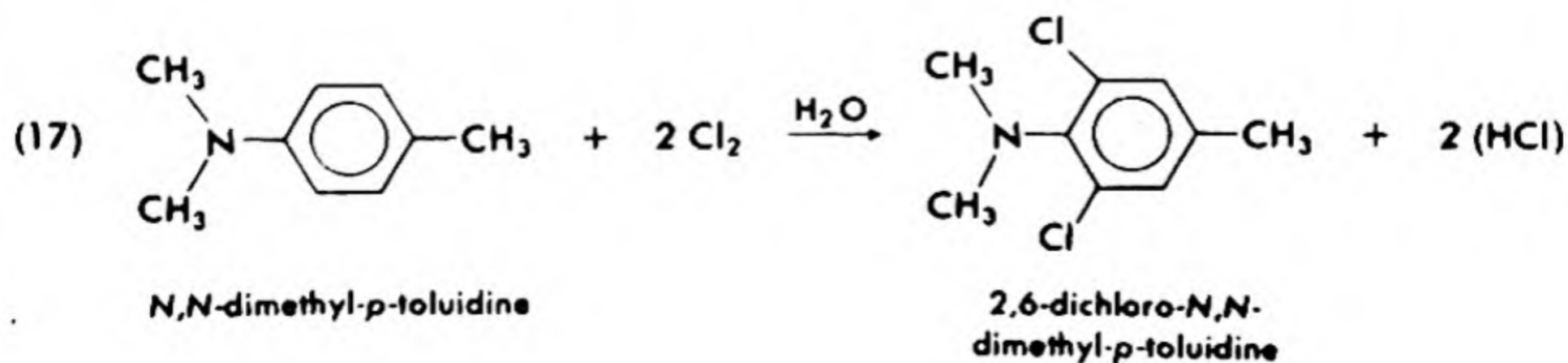
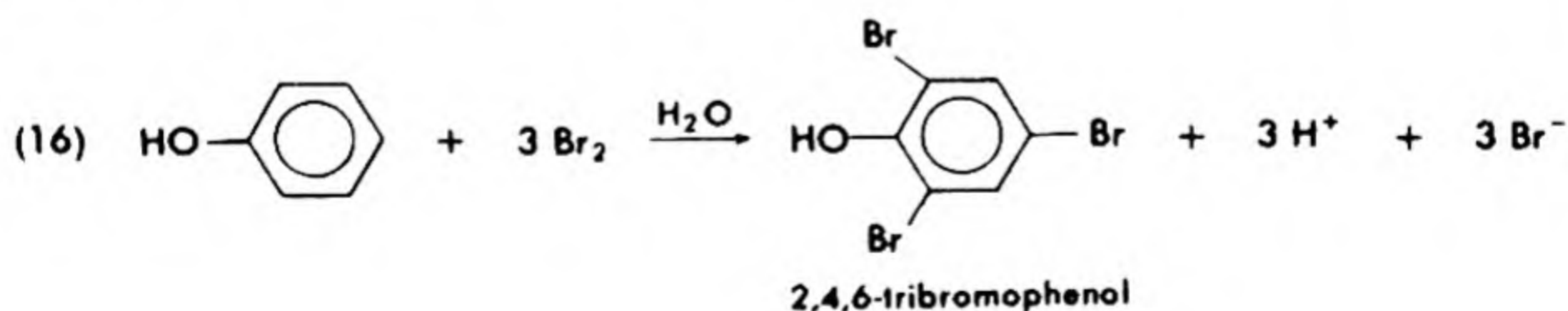
$$(12) \quad \text{rate} = k[\text{ArH}][\text{Cl}_2][\text{FeCl}_3]$$

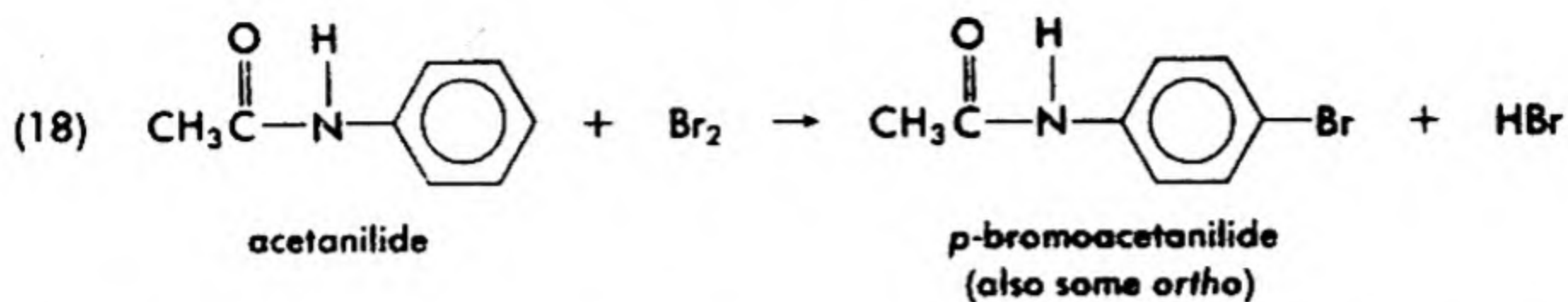
If the mechanism described in eqs. (9) to (11) is correct and if eq. (10) represents the rate-determining step, the reaction should have the kinetics shown in eq. (12), that is, the reaction rate should depend on the concentration of the aromatic compound, as well as that of chlorine and ferric chloride. If the aromatic compound is very inert, it is possible that an alternative mechanism may operate, in which the slow step represented by eq. (13), the formation of chlorine cations, followed by the faster step (eq. 14) together replace eq. (10). This mechanism predicts kinetics zero order in aromatic compound, as given in eq. (15).



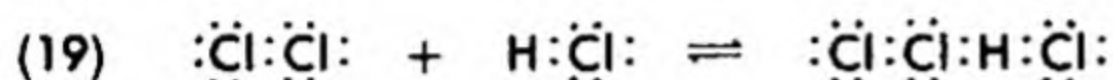
$$(15) \quad \text{rate} = k(\text{Cl}_2)^2(\text{FeCl}_3)$$

On the other hand, very active substrates (i.e., phenols, anilines, and their derivatives) require no catalyst. Even so mild an acid catalyst as water is sufficient to promote the replacement of *all ortho* and *para* hydrogen atoms in phenols and arylamines (eqs. 16–17). Acylation of an arylamine moderates the activating effect of the amino group enough to make stepwise substitution possible (eq. 18).





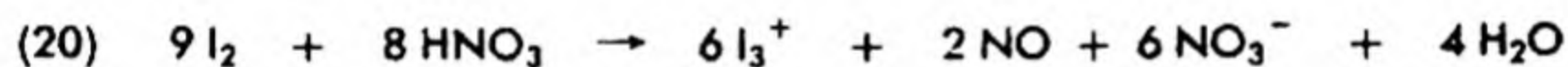
In such cases the aromatic substrate is nucleophilic enough to displace a halide ion from a halogen without the help of a Lewis acid. Reactions with halogens may be autocatalytic, as the hydrogen halide formed may serve as an acid catalyst by hydrogen bonding (eq. 19).



In summary, then, the reagent required for chlorination or bromination depends on the reactivity of the aromatic compound involved.

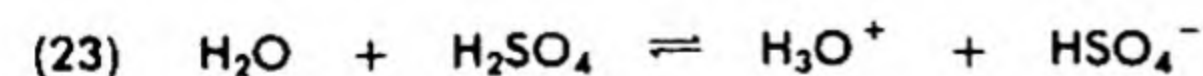
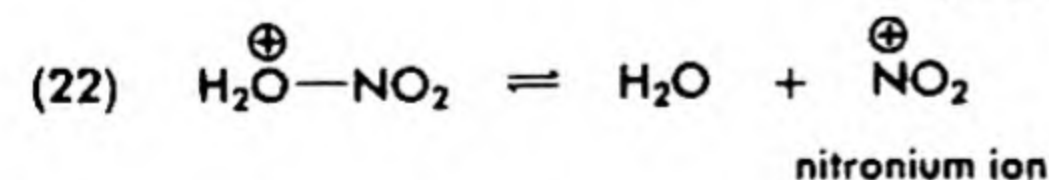
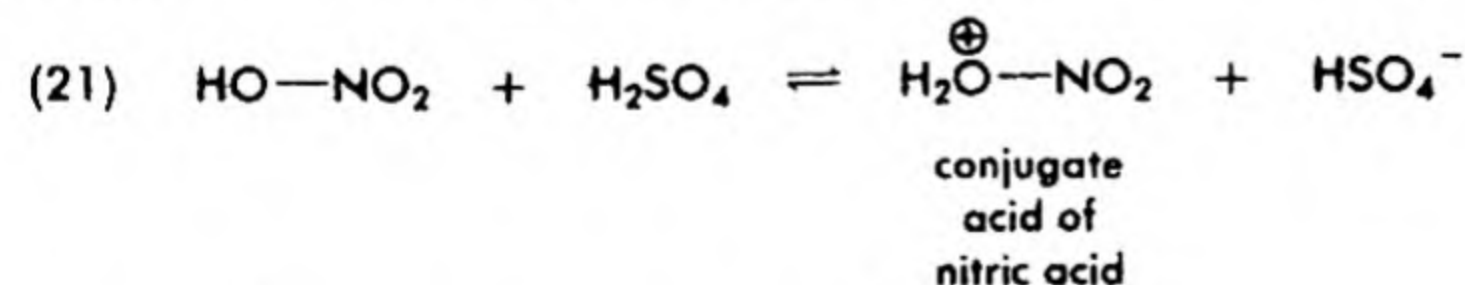
Aromatic fluorination is not carried out by direct substitution (see §24-2B).

Benzene and other aromatic hydrocarbons are not iodinated by iodine, either with or without Lewis acids present. Most iodides are prepared by reactions of diazonium salts (§24-1). However, benzene can be iodinated with iodine and dilute nitric acid. It seems most likely that iodine is oxidized to *iodine cations* (eq. 20), which are reactive enough to attack benzene rings.



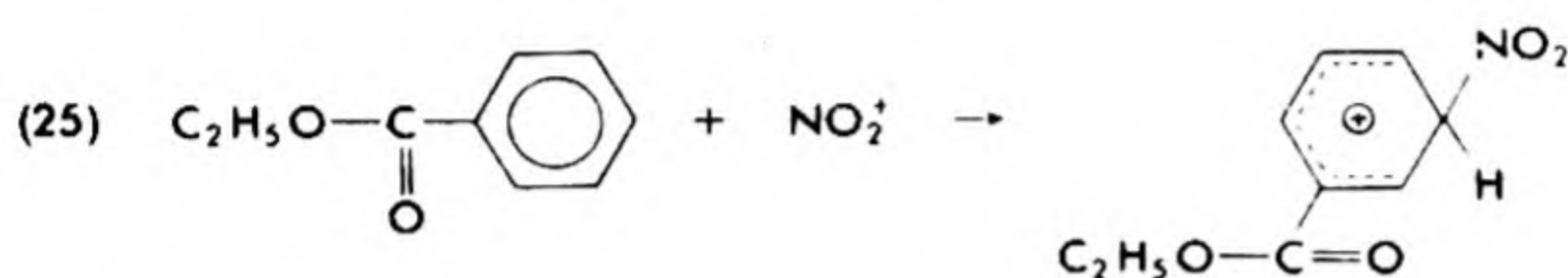
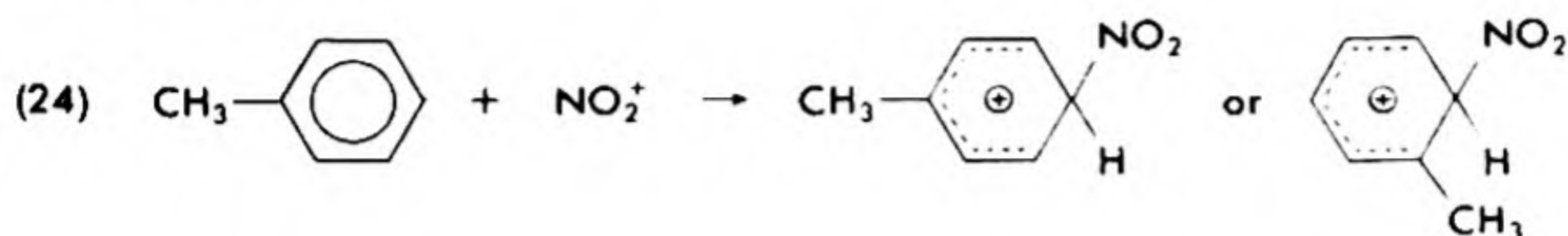
B. Reagents for Nitration

Concentrated nitric acid, fuming nitric acid, acetyl nitrate, and mixtures of nitric acid and sulfuric acid are used as nitrating agents. As might be anticipated, the strength of the reagent required decreases with increasing activity of the benzene ring. The actual nitrating species in acid solution may be nitric acid, the conjugate acid of nitric acid, or nitronium ion formed in sulfuric acid by the steps represented in eqs. (21) and (22).



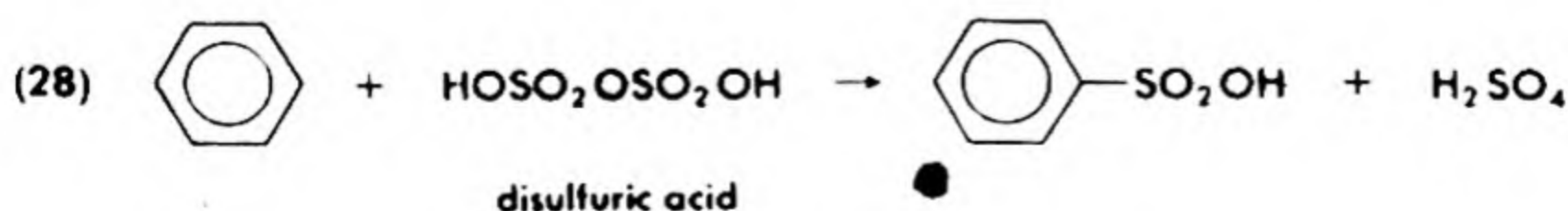
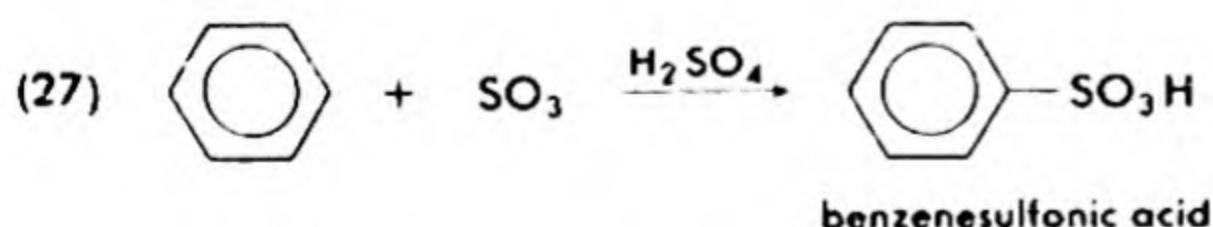
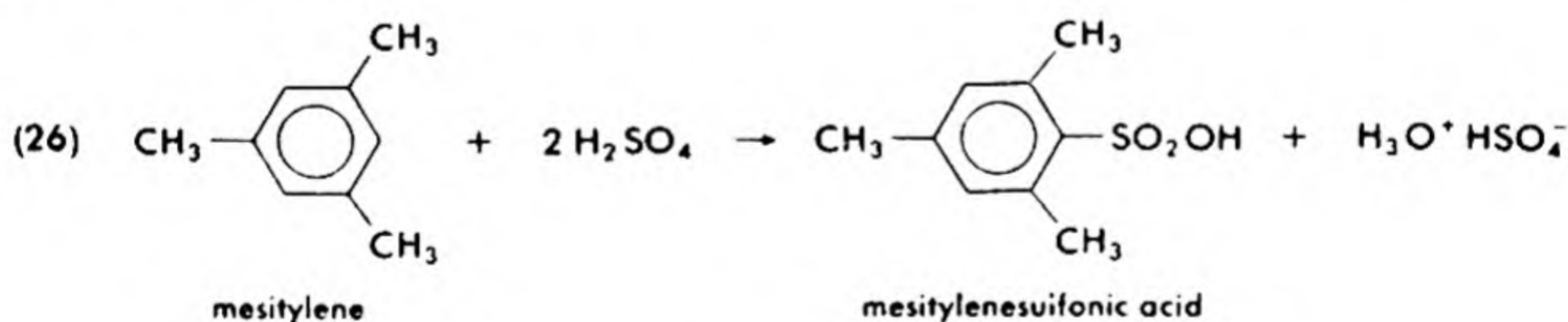
In 100% sulfuric acid, the formation of nitronium ion $:\ddot{\text{O}}=\text{N}^+=\ddot{\text{O}}:$ is essentially complete, as the water formed (eq. 22) is protonated as in eq. (23). In more dilute sulfuric acid (ca. 90%), this is not the case. If the

reaction of nitronium ion with aromatic substrate is faster than step (21), as in fact it is with toluene (outline 24), the rate of nitration is independent of aromatic substrate concentration. The analogous reaction with ethyl benzoate (eq. 25) is significantly slower than the rate of formation of nitronium ion, whereupon the reaction rate becomes first order in aromatic substrate.

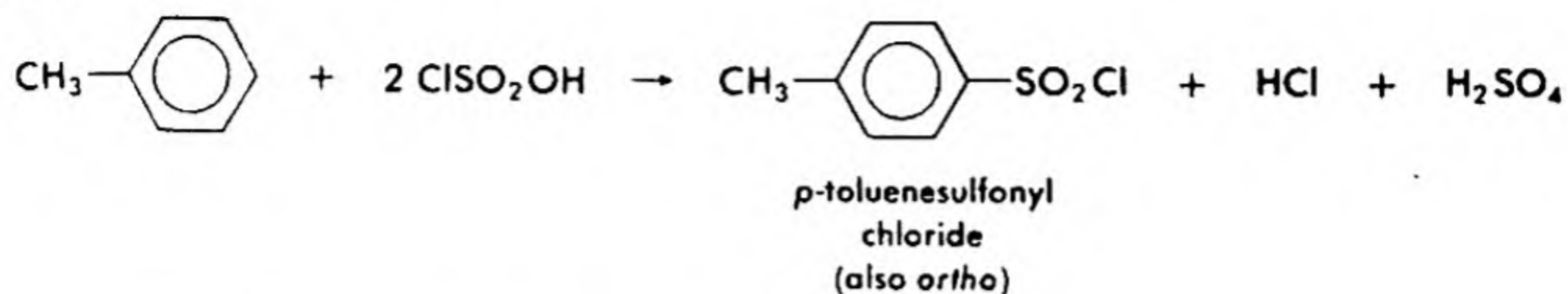


C. Sulfonating Agents

A variety of reagents can function as sulfonating agents. Highly reactive hydrocarbons, such as mesitylene, are readily substituted by concentrated sulfuric acid (eq. 26), while sulfonation of less reactive aromatic compounds requires mixtures of sulfur trioxide and 100% sulfuric acid. Whether the sulfonating agent is sulfur trioxide (eq. 27), or disulfuric acid, formed from sulfur trioxide and sulfuric acid (eq. 28), is not certain. Chlorosulfonation is a very useful reaction carried out with excess chlorosulfonic acid (eq. 29).



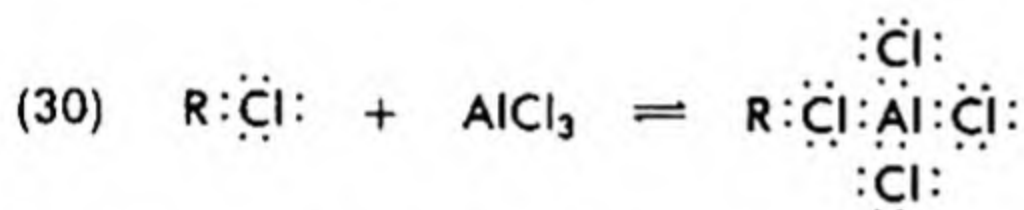
(29)



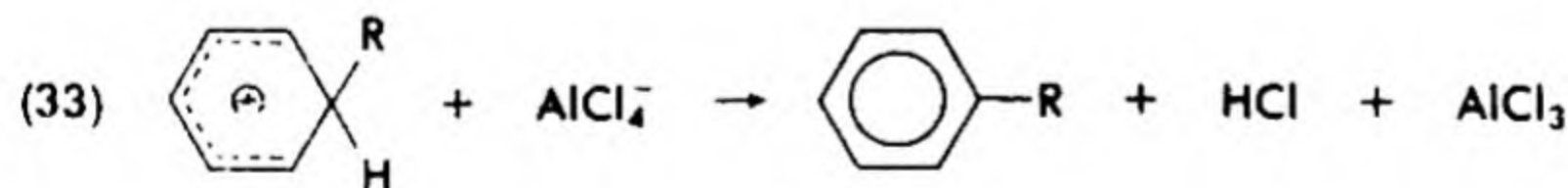
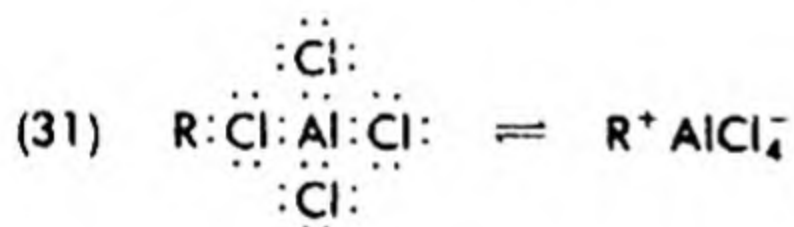
D. Friedel-Crafts and Related Reactions

The alkylation and acylation of aromatic compounds represent a very important class of organic reactions. Traditionally, the reactions involve the use of alkyl halides or acyl halides with aluminum chloride as catalyst. The detailed study of these reactions by Charles Friedel and James Mason Crafts (1874–1891) resulted in the association of their names with both types.

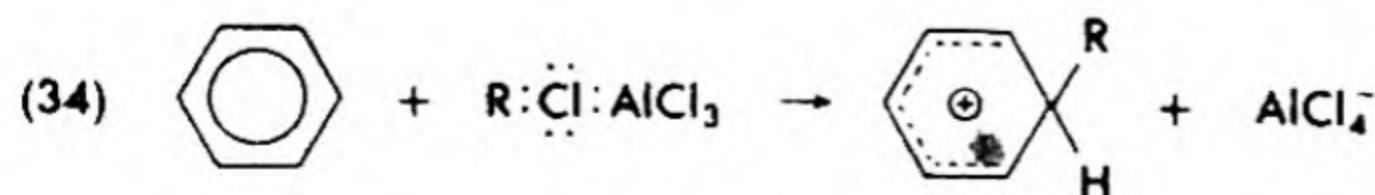
(1) *Alkylations.* For the alkylation reaction, two paths are possible. Both probably involve the formation of a complex between alkyl halide and aluminum chloride (eq. 30). This complex may now ionize to a carbonium ion and tetrachloroaluminate ion (eq. 31), followed by electro-



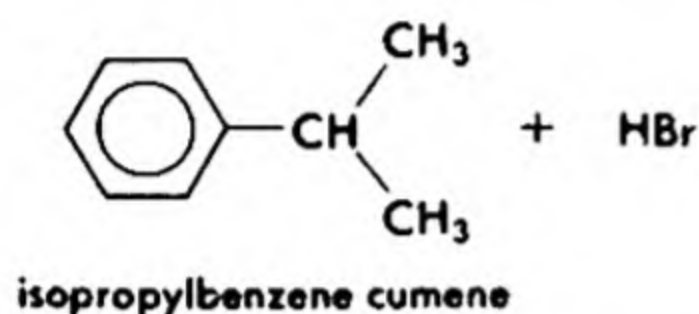
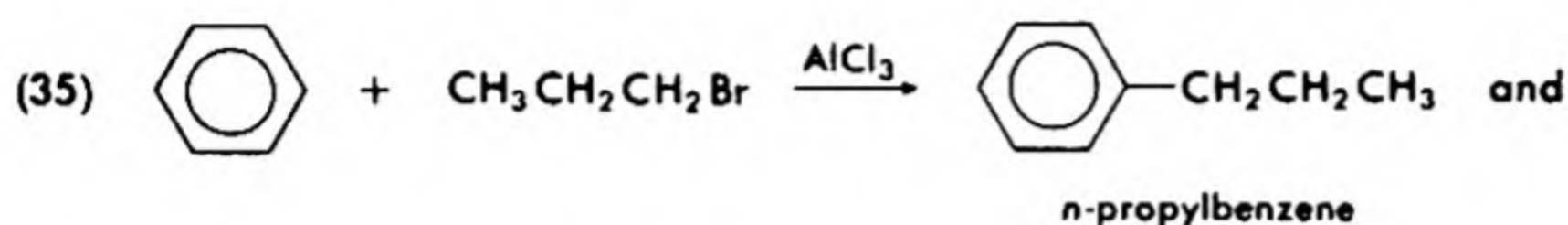
philic attack by R^+ on the aromatic nucleus (eqs. 32 and 33). This is



equivalent to an S_N1 reaction on the alkyl halide. An alternative mechanism involves a direct displacement on the complex by the aromatic substrate (eq. 34), followed by the step represented in eq. (33).

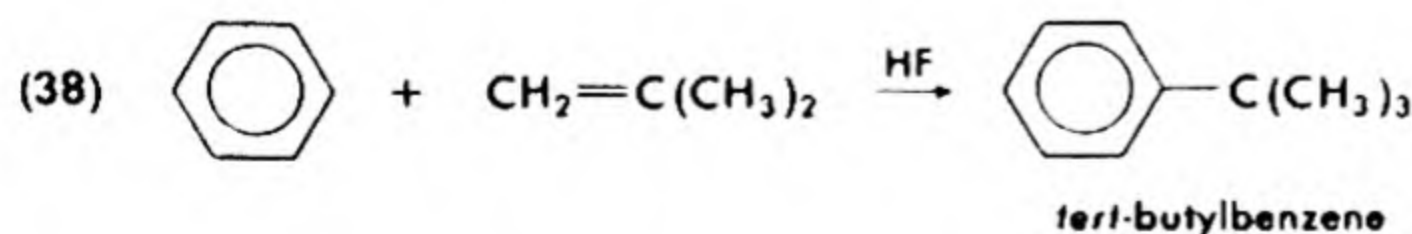
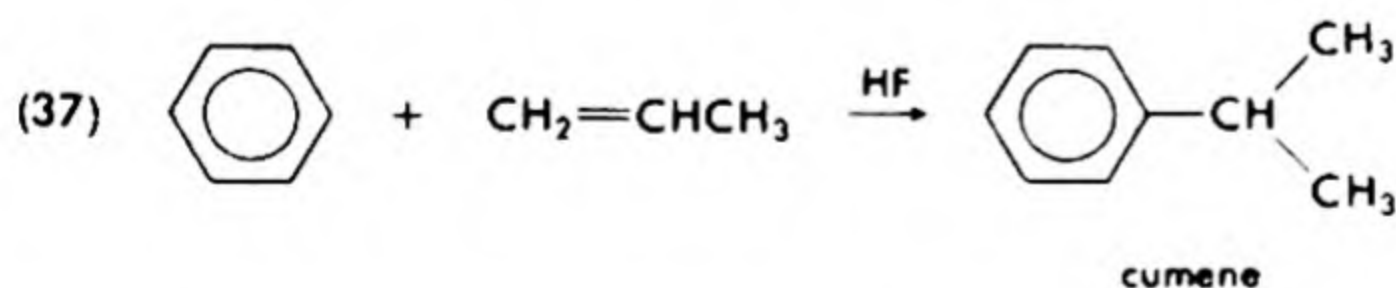
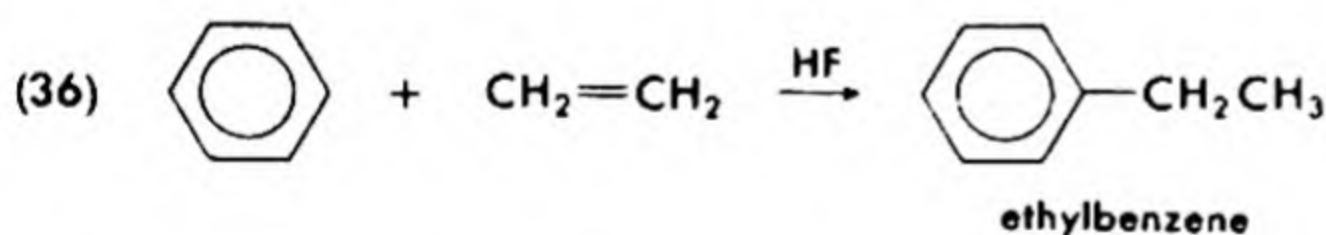


As the carbonium ion process is extensively utilized, rearrangements (see §12-2D) often attend Friedel-Crafts alkylations. Thus, treatment of benzene with *n*-propyl bromide and aluminum chloride gives a mixture containing some *n*-propylbenzene, but largely isopropylbenzene (outline 35). Such rearrangements severely limit the usefulness of the Friedel-



Craft alkylation. Rearrangements are not observed with tertiary halides (or with isopropyl), so that these alkylations are satisfactory as are those with methyl and ethyl halides. Occasionally, alcohols are used as alkylating agents with boron trifluoride as catalyst to minimize rearrangements.

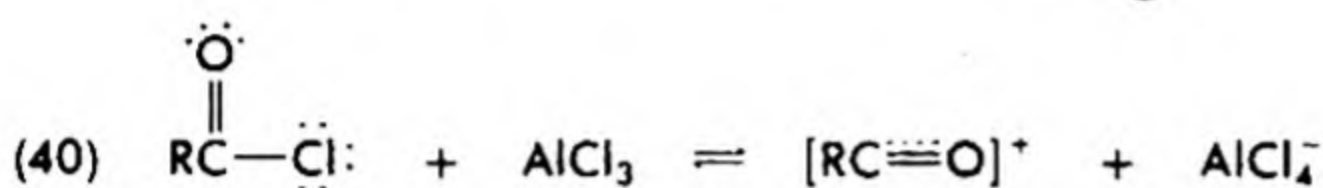
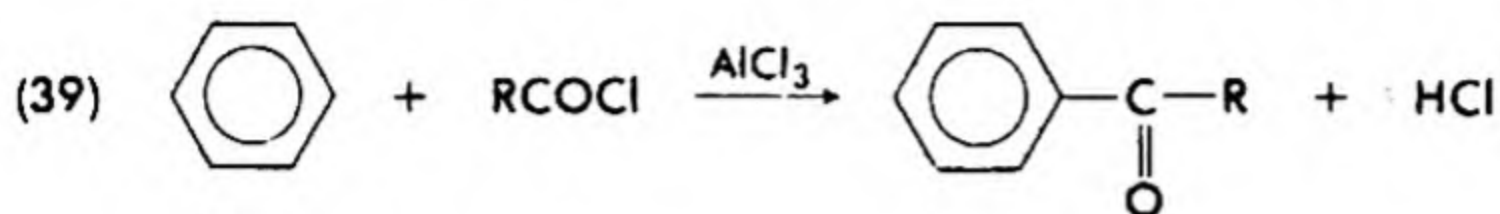
Alkylation of aromatic compounds with olefins is conducted industrially using hydrogen fluoride as catalyst. Thus, ethylbenzene is prepared from ethylene (eq. 36), cumene from propylene (eq. 37), and *tert*-butylbenzene from isobutylene (eq. 38). The additions follow the Markovnikoff rule. The largest use of ethylbenzene is dehydrogenation to styrene (§28-11), while cumene is used in high octane gasoline and as an intermediate in phenol synthesis (§7-3B).



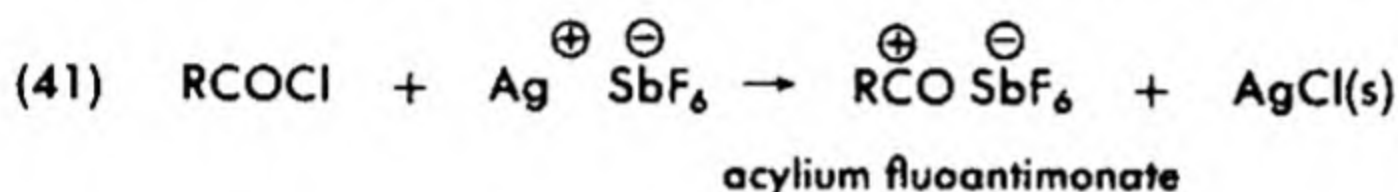
(2) **Acylation.** Treatment of aromatic hydrocarbons with acid chlorides and aluminum chloride gives good yields of aryl ketones (eq. 39). Alumi-

num chloride is stoichiometrically utilized, since the ketonic product complexes with aluminum chloride. The intermediate in the reaction is

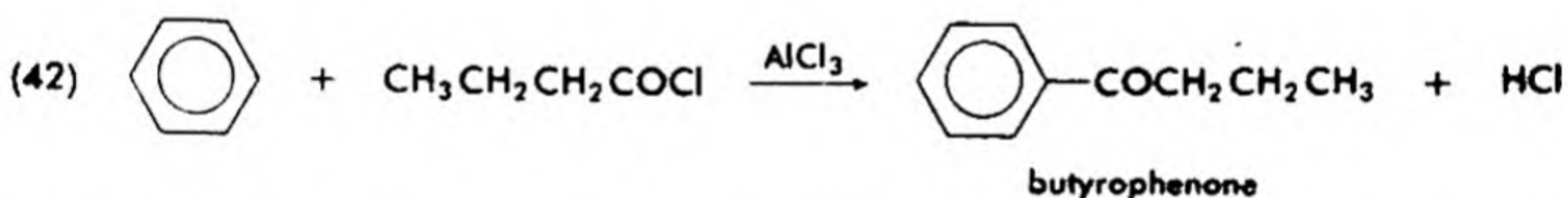
the acylium ion, $R-\overset{\delta+}{C}\equiv\overset{\delta+}{O}$, produced as in eq. (40), which then attacks the aromatic ring in the usual fashion. Recently, it has been possible to



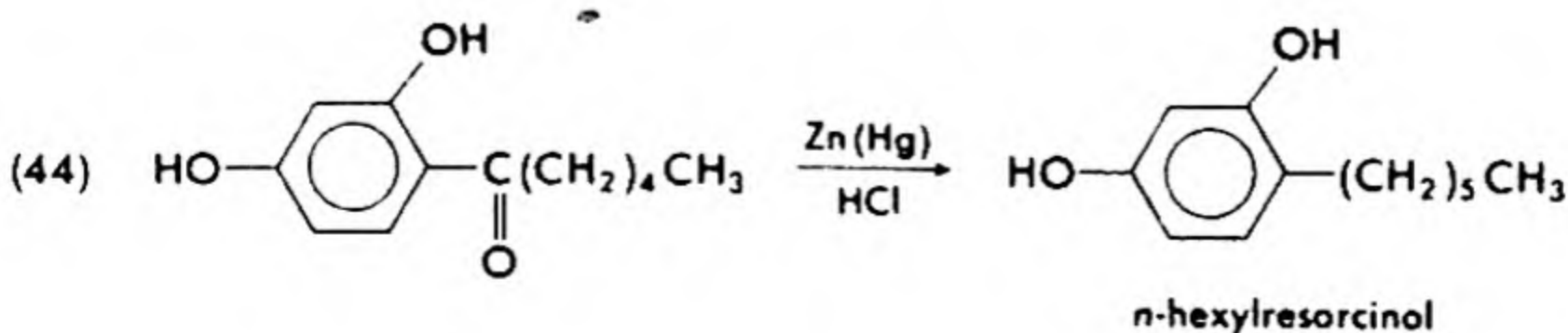
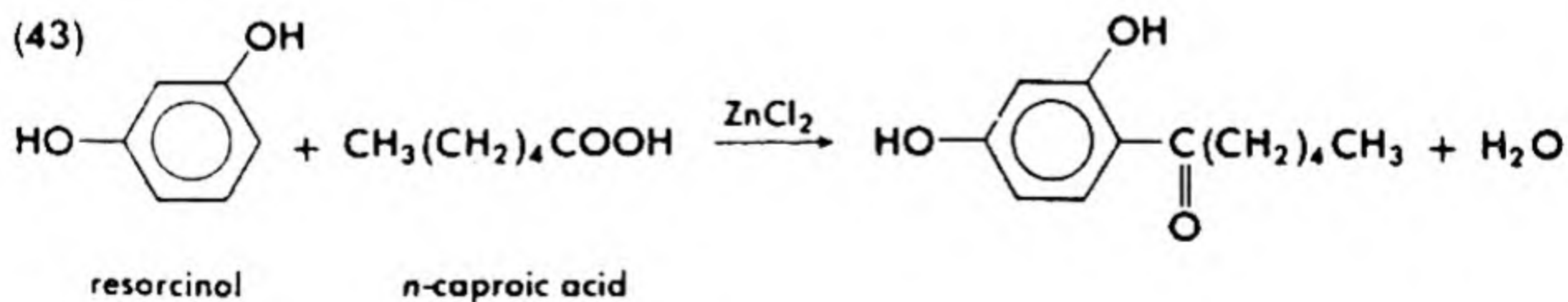
prepare stable acylium salts (eq. 41), which can be used in acylation reactions. Acylium ions have little tendency to rearrange so that acylation can be carried out with any acyl halide. Thus, *n*-butyryl chloride gives



n-butyrophenone (eq. 42). As ketones can be reduced by the Clemmenson or Wolff-Kishner reductions (see §28-2A and §24-4) to hydrocarbons, this sequence provides a useful synthesis of alkylbenzenes.

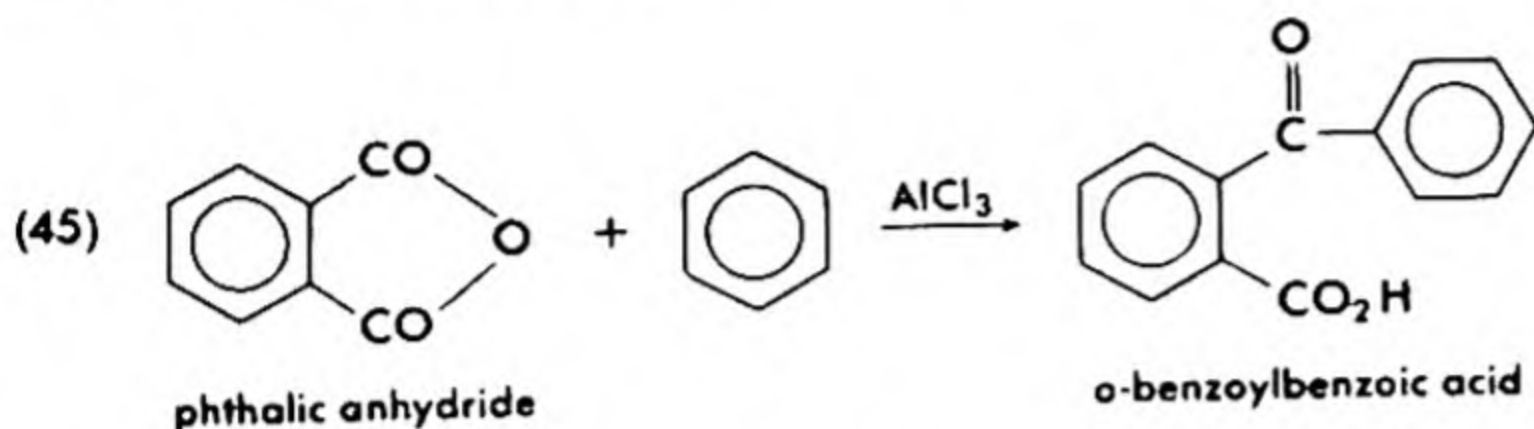


With very reactive aromatic substrates, the weaker Lewis acid, zinc chloride, may replace aluminum chloride, and the free acid may replace the acid chloride. Thus, resorcinol and *n*-caproic acid (eq. 43) react; the product, reduced by the Clemmenson procedure (eq. 44), gives *n*-hexylresorcinol, a useful antiseptic.

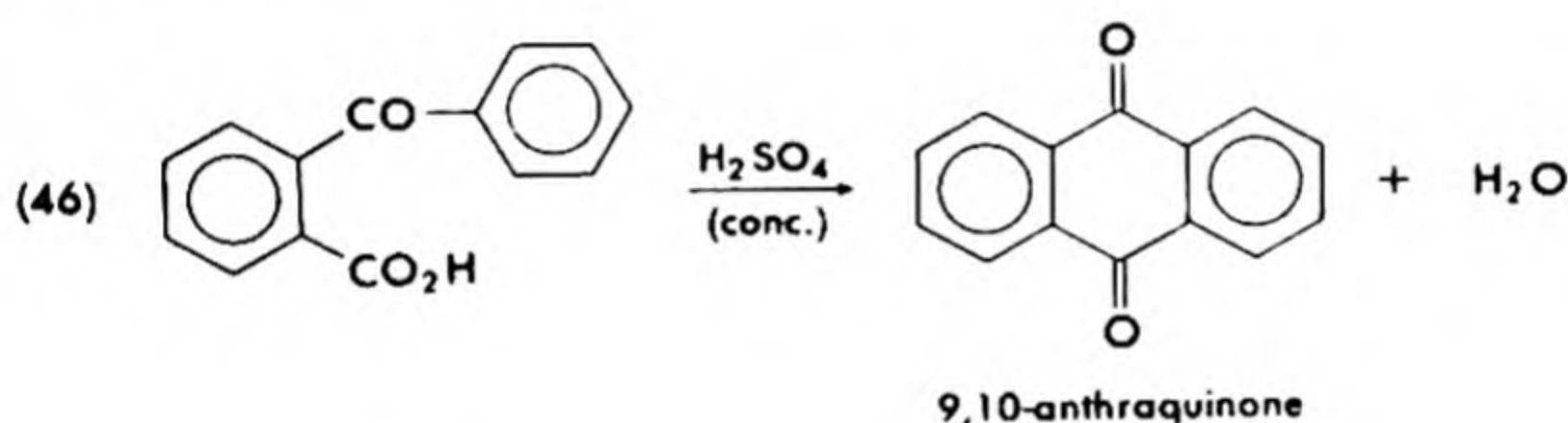


However, highly deactivated aromatic rings, such as that in nitrobenzene, fail to undergo acylation even with aluminum chloride. Even in the absence of deactivating substituents only one acyl group is usually capable of being placed on a ring.

Acid anhydrides can be used as well as acid chlorides. Thus, phthalic anhydride and benzene give *o*-benzoylbenzoic acid (eq. 45).

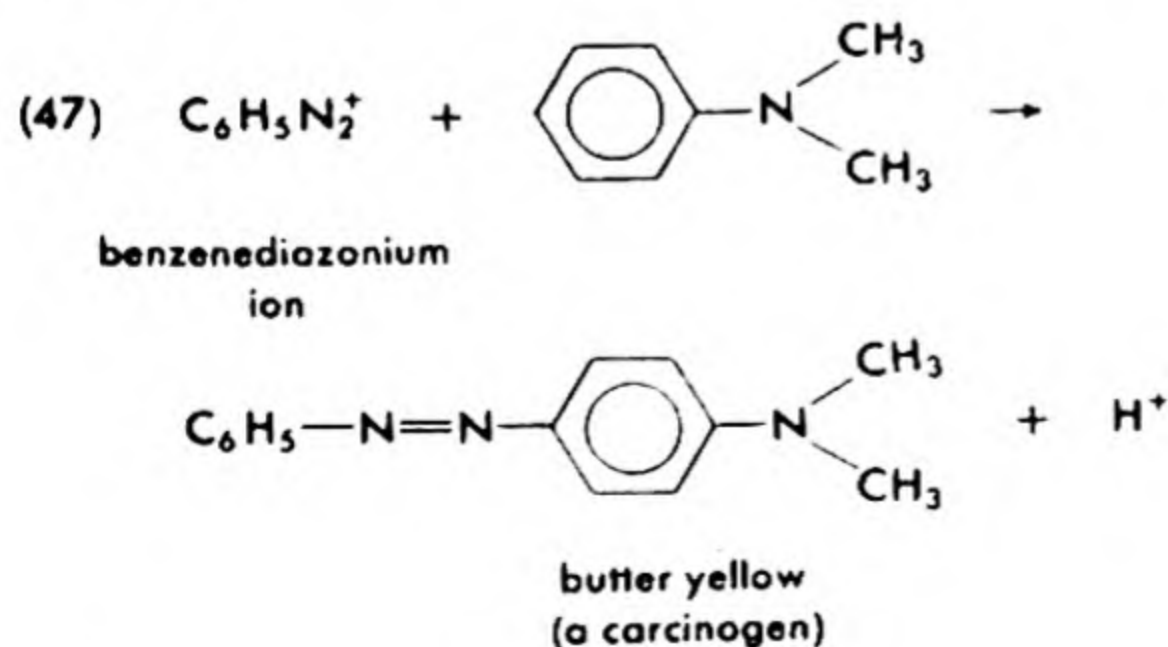


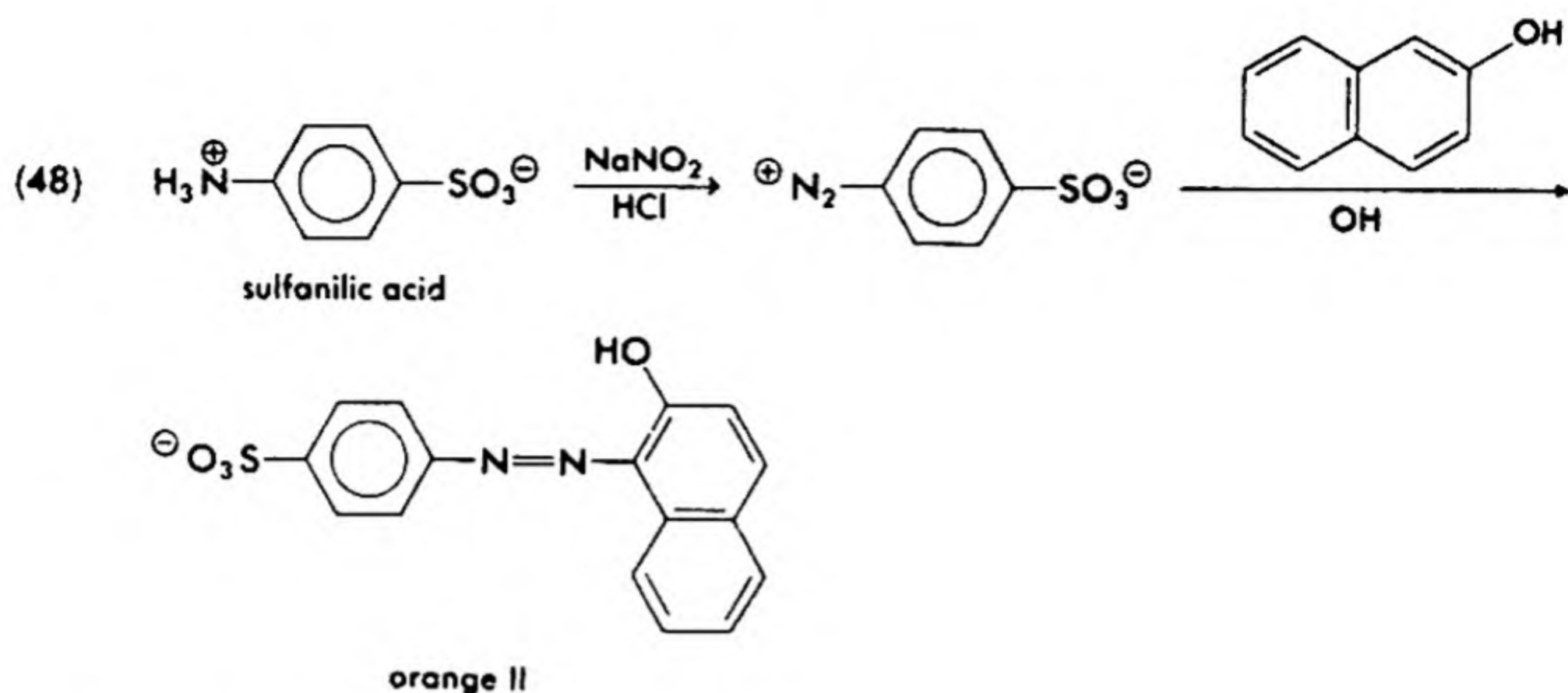
Ring closures go readily when five- or six-membered rings are formed. For these, one may use acid chlorides and aluminum chloride, or acids and sulfuric acid or hydrogen fluoride. The formation of anthraquinone (eq. 46) is quantitative.



E. Azo Coupling Reactions

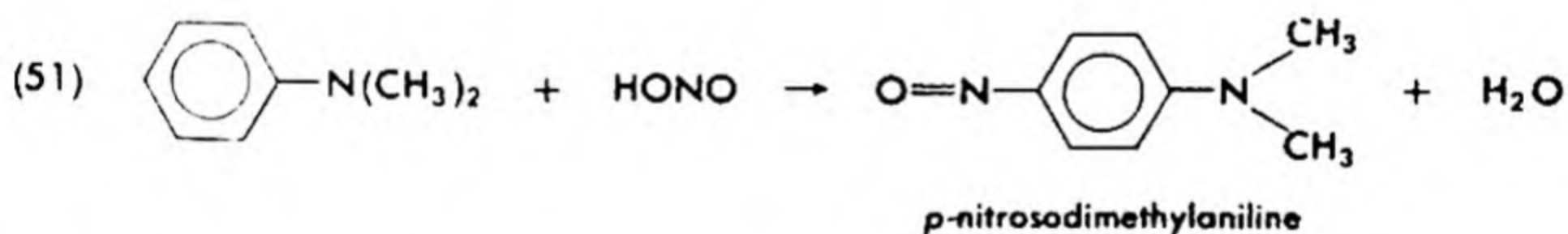
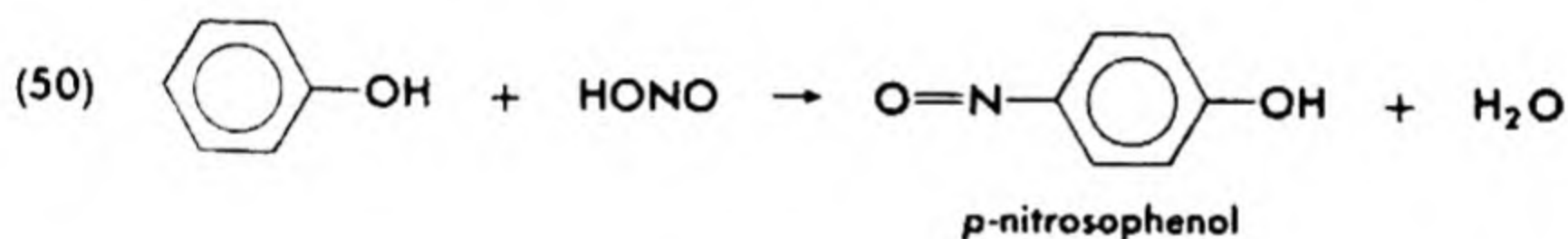
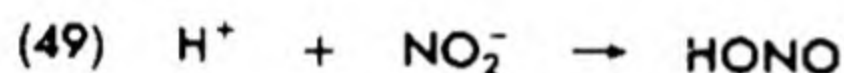
Very reactive species, such as phenols and aromatic amines, can undergo electrophilic substitution by arenediazonium ions, which are too weak to attack other aromatic compounds. This reaction is fundamental to the synthesis of azo dyes. Examples are given in eq. (47) and outline (48).





F. Nitrosation

Nitrous acid, prepared *in situ* from sodium nitrite and dilute mineral acid, and esters of nitrous acid, such as amyl nitrite, are weak electrophiles which attack only phenols, some aryl ethers, and aromatic tertiary amines (eqs. 50 and 51).



16-4 SUBSTITUENT EFFECTS

Groups already on an aromatic ring markedly influence the stability of the various sigma complexes that may be formed as intermediates. Thus, these groups not only direct entering substituents into certain preferred positions, but also either increase or decrease the rate of the reaction as a whole.

A reaction coordinate diagram for aromatic electrophilic substitution on benzene is given in Fig. 16-2. This is a typical diagram for a reaction in which an intermediate is involved (see §11-3E). The intermediates are the sigma complexes discussed in §16-1. The transition state energy barrier for this reaction is that labeled TS_1 in the figure; this assumes formation of the intermediate to be rate-determining.

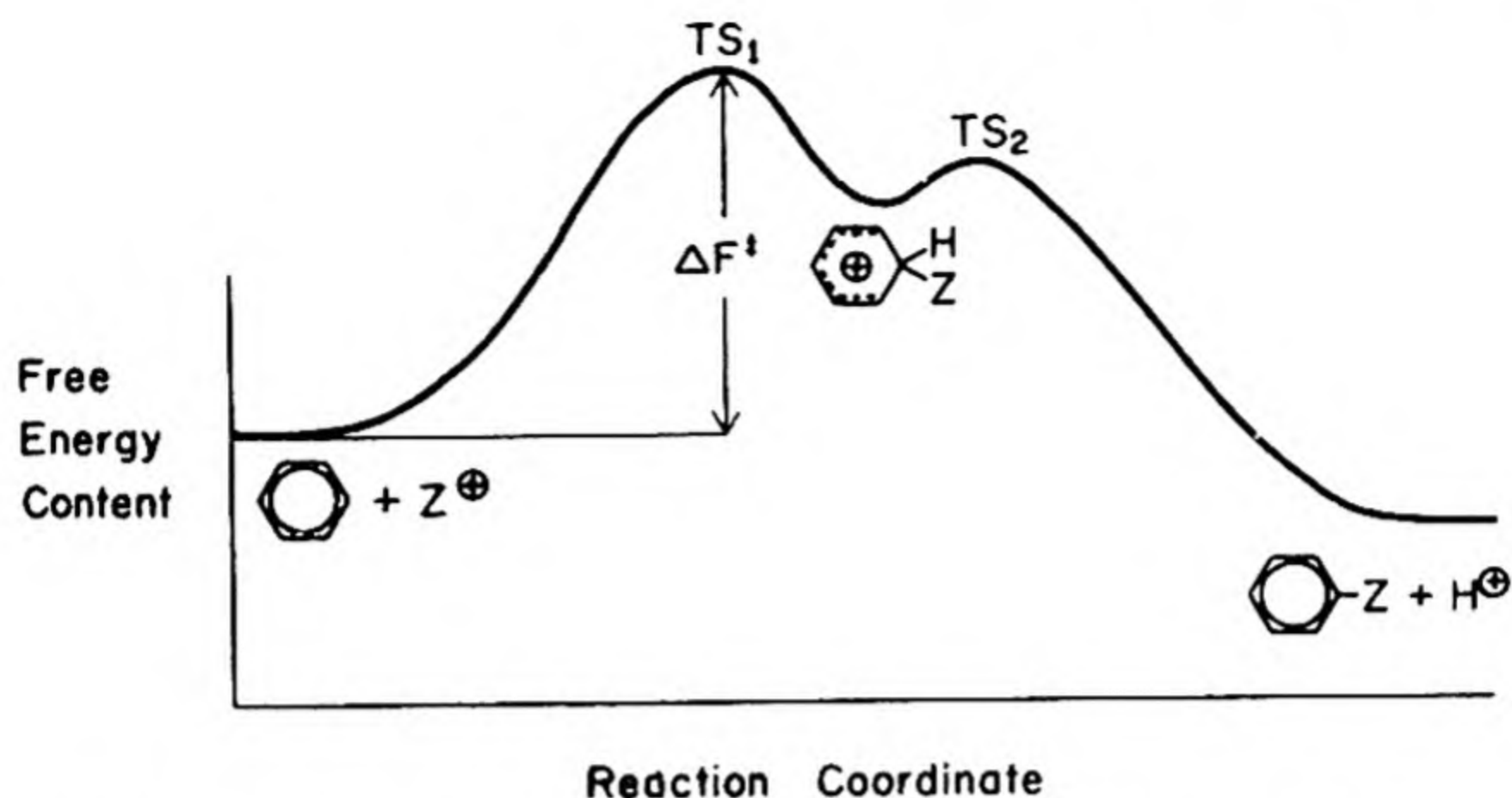


Fig. 16-2. Energy Profile for an Electrophilic Aromatic Displacement Reaction.

As we have noted before, the rate of the reaction depends on the free energy of activation, which is the difference between the energy of the transition state and the ground state of the reactants. By a consideration of the effects of substituents on these two energies, one should be able to understand both reactivities in aromatic substitution and the orientation rules that result from these reactivities. First of all, one should note that the reactivity of benzene is the sum of the reactivities of all of the six identical positions (Fig. 16-3). For a monosubstituted benzene, the reactivities (partial rate factors) of all positions are no longer identical; the total rate thus is the sum of twice the rate factor at each *ortho* position, plus twice the rate at each *meta* position, plus the rate at the *para* position.

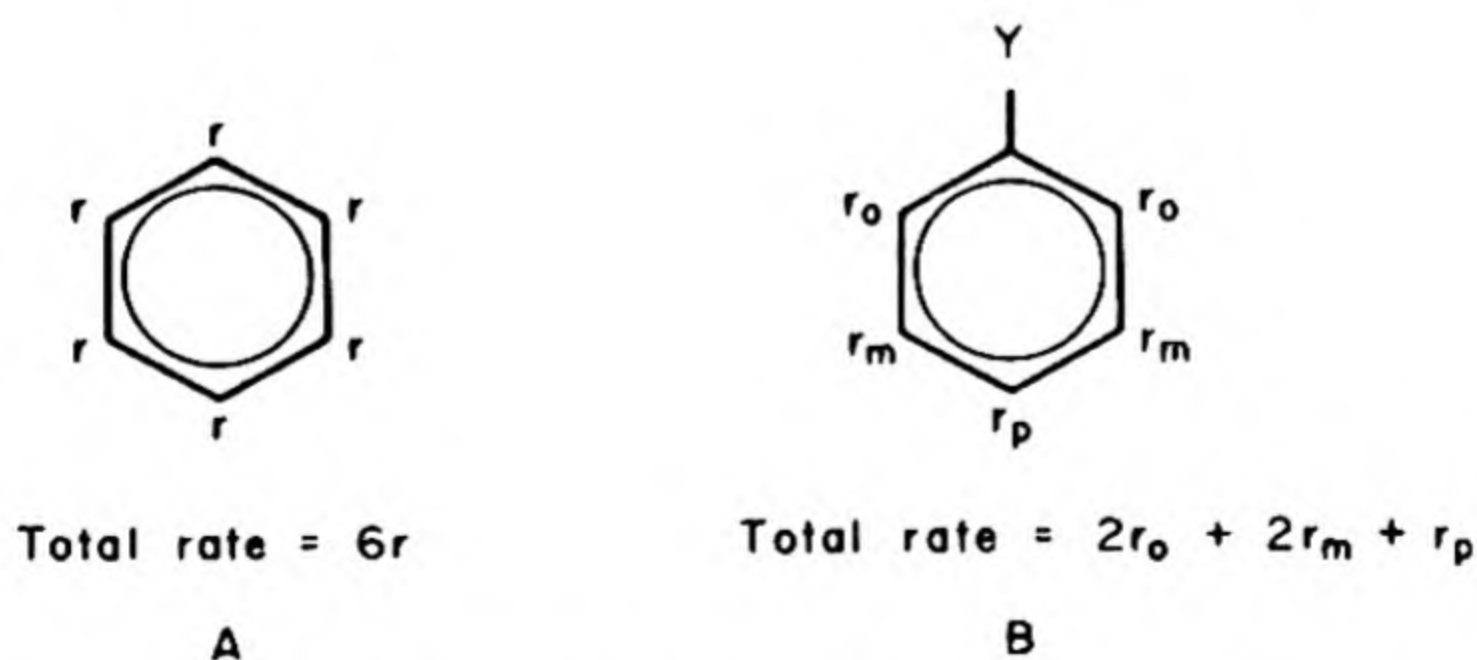
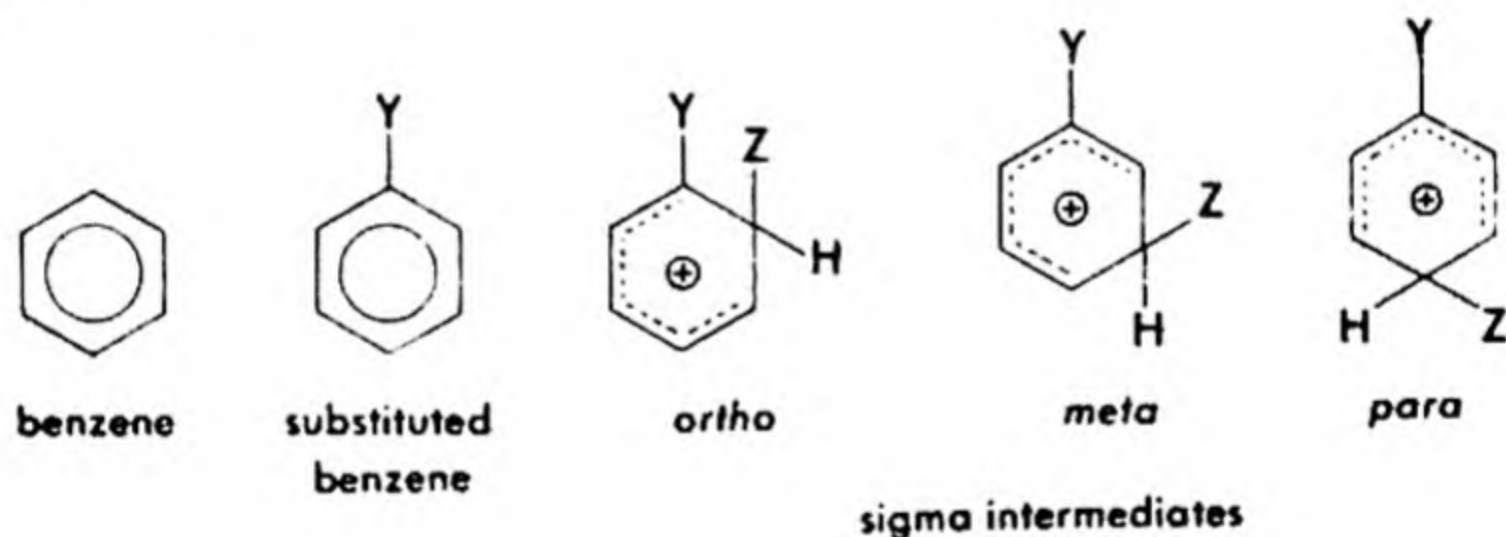


Fig. 16-3. Distribution of Partial Rate Factors. (A) Substitution into benzene, (B) Substitution into a monosubstituted benzene.

The total rate for a monosubstituted benzene may be greater (ring activation) or less (ring deactivation) than that of benzene.

If a compound is more reactive than benzene, the weighted value of ΔF^\ddagger must be less than that for benzene; the converse is also true. It is necessary to consider the effect of a substituent on the relative free energies of the *ortho*-, *meta*-, and *para*-substituted transition states as well as its effect on the free energy of the ground state in order to rationalize substituent effects on rates and orientation. Having no better choice, we shall consider the intermediate sigma complexes to approximate the transition states.

The problem divides itself into two parts. The first is the effect of a substituent on stability of the ground state (note that *the ground state is identical for substitution ortho, meta, or para to the substituent*) compared with benzene, and the second is the effect on the stabilities of the various possible intermediates. A substituent which stabilizes one or more of the transition states more than it does the ground state increases the reactivity at that (or those) positions over benzene; one which stabilizes the ground state more than the transition states decreases the reactivity at such positions. As usual, substituents can affect stability by electrical or steric effects or both.

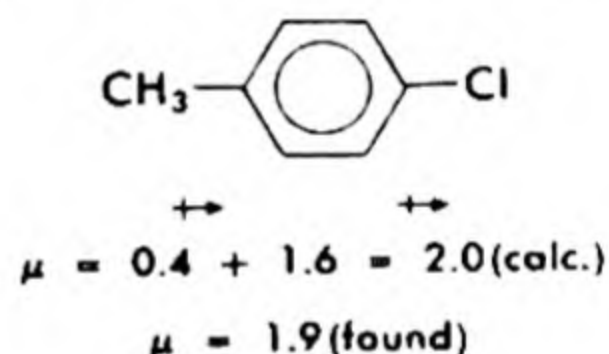
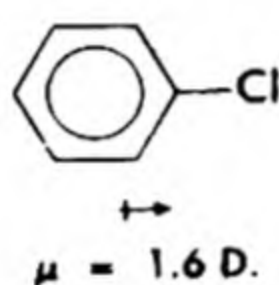
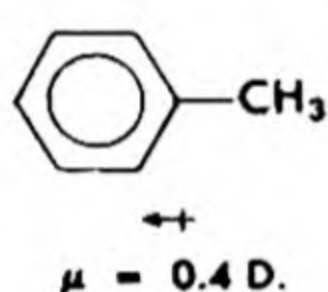


Electrical effects are treated in much the same way as in electrophilic addition to olefins (see §14-2B) or as discussed in the chapter on acid strengths (see §10-2C–§10-2F) and include inductive and resonance effects. Resonance effects always stabilize the ground states of the aromatic compounds, but may have much larger effects on the transition states. Those transition states which have the largest stabilization are formed faster. Overall rate and orientation consequences follow. In certain cases electrical effects destabilize the transition state. In such cases reaction proceeds mainly through those transition states with the least unfavorable electrostatics.

Before considering the effects on transition states, it is useful to consider those on ground states. Here the section (§7-3A) on resonance in benzene should be reviewed. There we have treated benzene as a system in which the ring involves six σ bonds and a symmetrical π system containing six

electrons in three bonding π orbitals. Now, the effect of locating a substituent on the ring is to alter the symmetry of both the π and σ electron systems through conjugative and inductive effects. This not only changes electron distribution and stability, but also has consequences on dipole moments (§9-2C), bond lengths, and other physical properties. We can get some idea about the operation of such effects by comparing dipole moments in saturated aliphatic molecules with those in aromatic systems. In saturated systems, only inductive effects can operate. A comparison of these with conjugated systems or aromatic systems gives a measure of conjugative resonance effects. The dipole moment is a vector, the measurement of which (§35-1) gives only its magnitude. It is possible to tell the direction of the moment by the additivity principle, however, as we shall see.

Scrutiny of the data in Table 16-1 shows, as anticipated, that molecules with complete symmetry have zero dipole moment (e.g., benzene and methane). In toluene, however, the dipole moment, μ , = 0.4 D.; we do not know from these data whether the electrons are shifted toward the phenyl ring or away from it. In chlorobenzene we may assume that the dipole has its negative end toward chlorine. *p*-Chlorotoluene would be


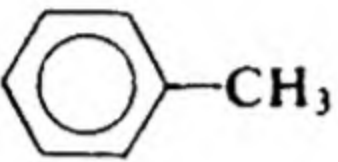
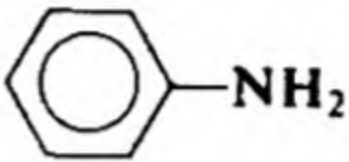
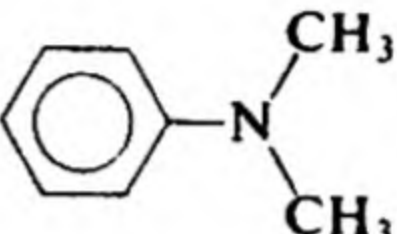
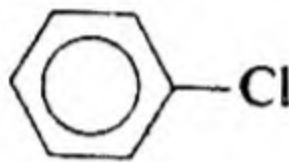
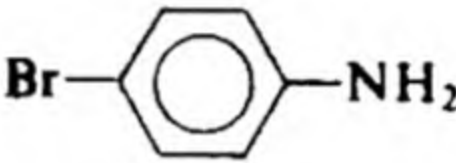
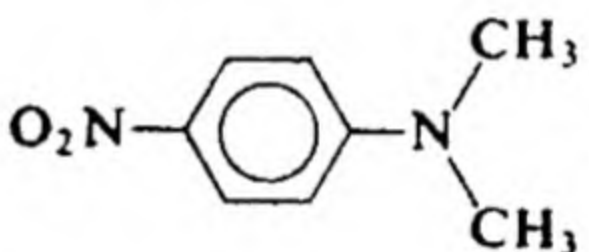
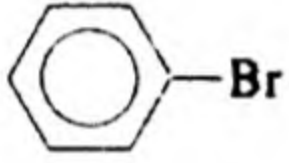
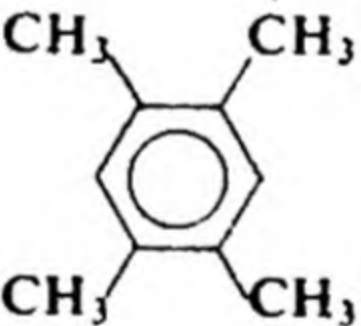
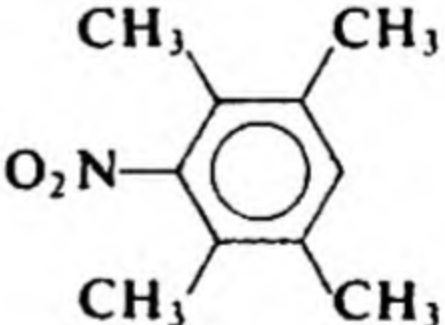
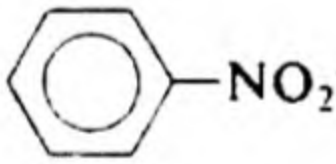
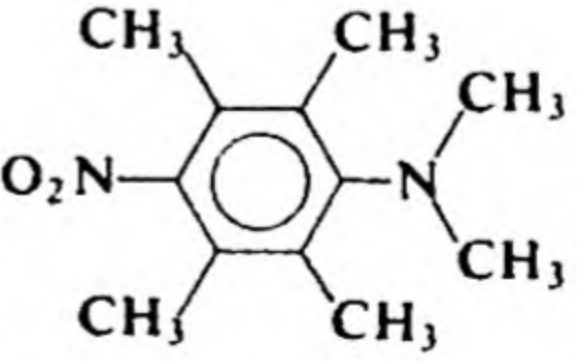
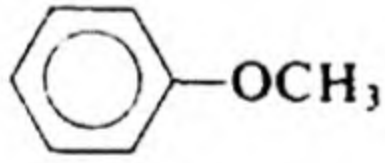
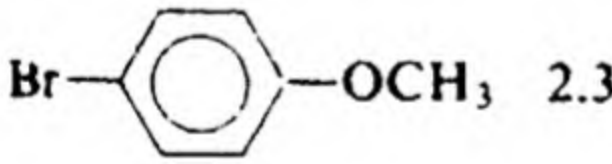


expected to have a dipole moment of 1.2D.(1.6 – 0.4) if the individual bond moments were in opposite directions, and one of 2.0 D. (1.6 + 0.4) if they were in the same direction. The value of 1.9D. observed shows that phenyl is electron-attracting compared with methyl. This confirms our deduction made on the basis of acid strengths (§10-2A).

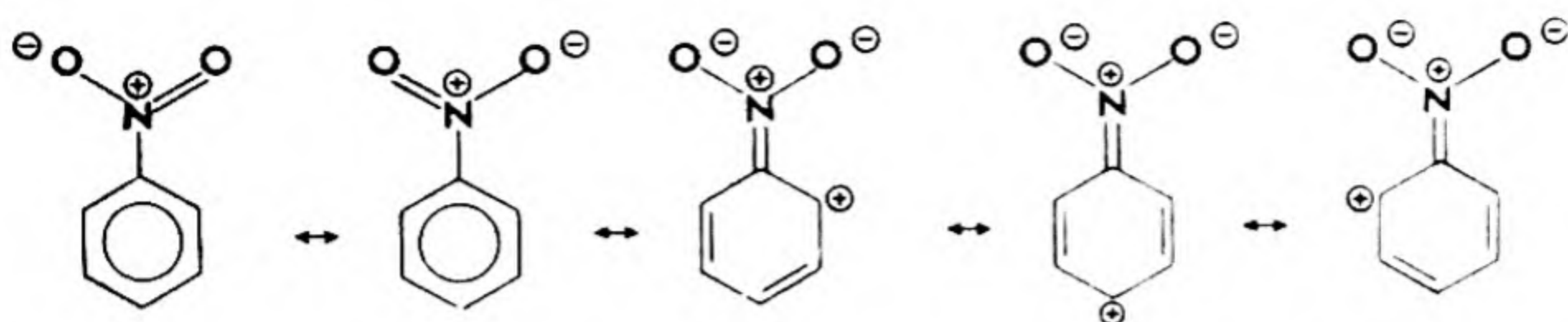
The discussion in the previous paragraph shows that, compared with benzene, toluene has more electron density in the ring, chlorobenzene less. Note that this is an experimental fact independent of theoretical arguments. A comparison of methyl chloride and chlorobenzene and of methyl bromide and bromobenzene indicates that their dipole moments are largely consistent with inductive effect additivities.

Nitrobenzene and nitromethane, on the other hand, represent systems in which strong resonance effects appear. Without resonance effects, one would predict that nitrobenzene would have a somewhat smaller dipole moment than nitromethane, that is, around 2.6–3.0 D. This is not the case, however, as nitrobenzene has the larger dipole moment. This is ordinarily explained by assuming the following valence bond structures

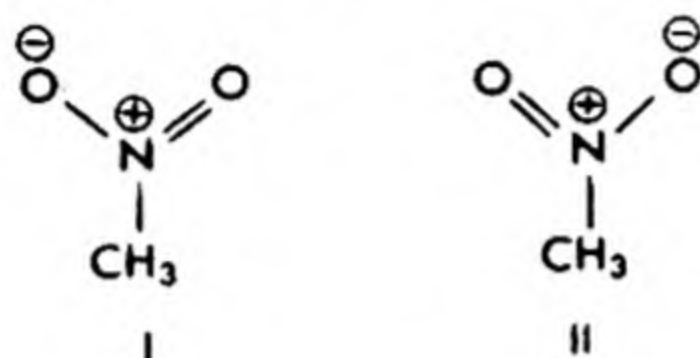
TABLE 16-1. Dipole Moments of Some Derivatives of Methane and of Benzene.

Compound	μ , D. ^a	Compound	μ , D.
CH ₄	0.0	CH ₃ NH ₂	1.2
	0.0	CH ₃ N(CH ₃) ₂	0.7
	0.4		1.5
CH ₃ Cl	1.8		1.6
	1.6		2.9
CH ₃ Br	1.8		6.9
	1.5		0.0
CH ₃ NO ₂	3.0		3.4
	4.0		4.1
CH ₃ OCH ₃	1.3		
	1.2		
	2.3		

^aDebye units, e.s.u.-cm. $\times 10^{18}$, see §9-2C.



in nitrobenzene, which makes the charge separation greater than in nitromethane, where the only important canonical structures are I and II.



Conjugation in nitrobenzene requires the nitrogen and oxygen atoms to be coplanar with the ring as the ring-nitrogen bond has double-bond character. If this is made impossible by placing methyl groups in *ortho* positions, thus twisting the nitro group out of the plane of the ring, the dipole moment is decreased. Compare nitrodurene, only 3.4 D., and nitrobenzene, 4.0 D. This is termed *steric inhibition of resonance* (see Fig. 16-4). Note also that the ring is electron-deficient in nitrobenzene compared with benzene.

Methyl ether and anisole have dipole moments of equal size, and one might guess (incorrectly) that the direction is similar.

The value for methyl ether is the resultant of two methyl-oxygen bond moments, which one may calculate using vector analysis. Oxygen is at the negative end of each bond dipole and thus at the negative end of the

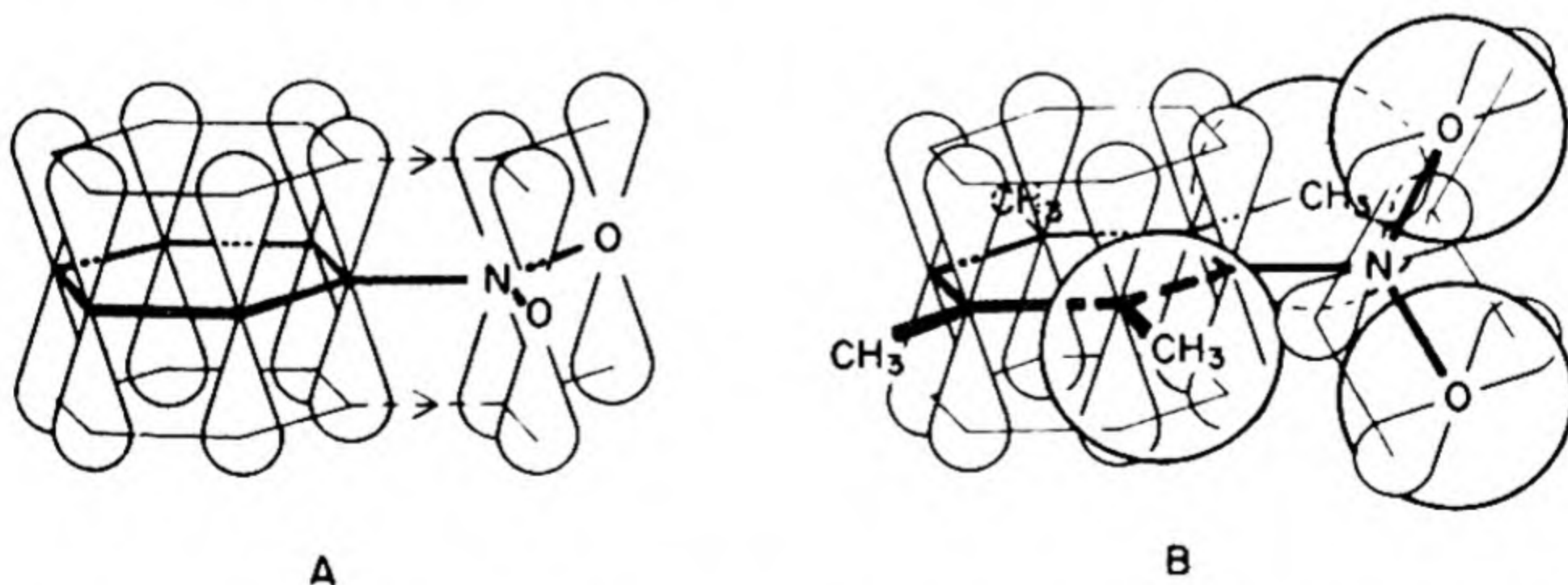
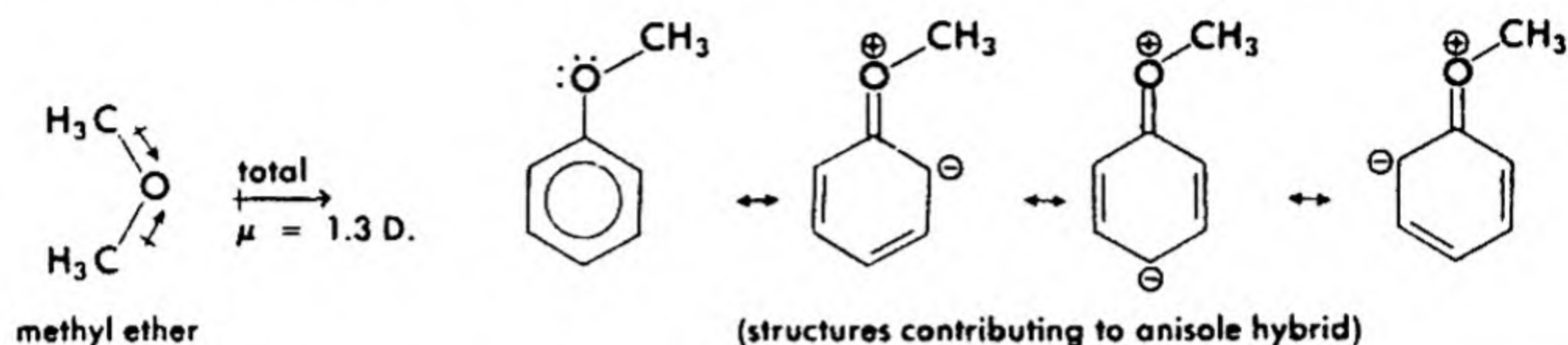


Fig. 16-4. Steric Inhibition of Resonance. (A) Conjugation of nitro group with ring in nitrobenzene, (B) Prevention of conjugation in nitrodurene by interference between *ortho* methyl groups and oxygen atoms. Twisting of nitro group out of ring plane prevents π orbital overlap.

molecular dipole. The opposite direction of the dipole in anisole is shown by the value for *p*-bromoanisole, $\mu = 2.3$ D. Only if the dipole involves electron donation from the oxygen to the ring can this be correct (§35-2A).



Data on amines and aniline derivatives correspond with those of oxygen derivatives in that these groups donate electrons to the ring, and that the ring is electron-rich compared with benzene. Comparison of the data on anilines, dimethylanilines, and durene derivatives (Table 16-1) gives additional evidence for steric inhibition of resonance.

Those groups that furnish electrons to the ring correspond closely with those that activate the ring toward electrophilic substitution (§16-4). Similarly, ring-deactivating groups correspond closely with those that withdraw electrons from the ring. That this should be the case is perhaps obvious, as in the transition state for electrophilic displacement, the ring is depleted of an electron pair. Some relative reactivities are given in Table 16-2.

A. Orientation of the Entering Groups

While one can show by a consideration of resonance structures that positions *ortho* and *para* to many groups have an excess or deficiency of π

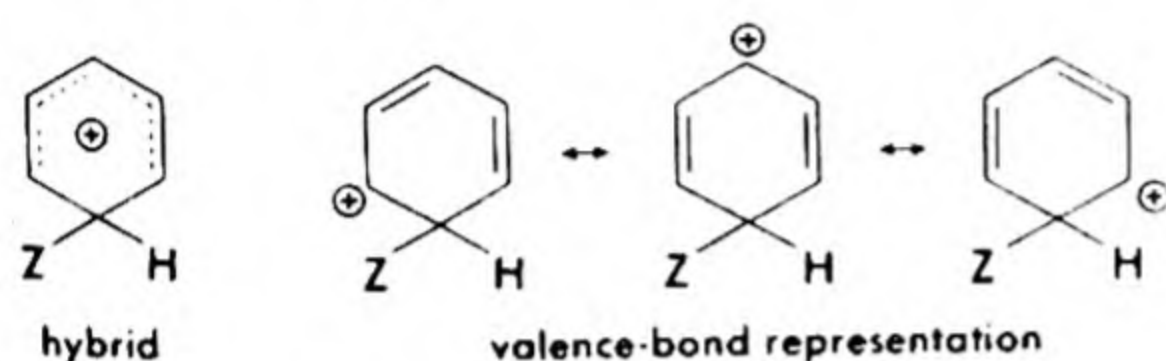
TABLE 16-2. Relative Reactivities of Aromatic Compounds Toward Nitration. Partial Rate Ratios at Various Positions (Corrected For Number of Positions)

Compound	$\frac{r_o}{r_{C_6H_6}}$	$\frac{r_m}{r_{C_6H_6}}$	$\frac{r_p}{r_{C_6H_6}}$	r Total
Benzene	1	1	1	6
Toluene	42	2.5	58	147
3°-Butylbenzene	5.5	4.0	75	94
Chlorobenzene	0.03	0.00	0.14	0.20
Bromobenzene	0.037	0.00	0.106	0.18
Iodobenzene	0.22	0.002	0.63	1.08
Nitrobenzene	3×10^{-6}	4×10^{-5}	3×10^{-7}	8.6×10^{-5}
Chloromethylbenzene (Benzyl chloride)	0.20	0.14	0.95	1.63
Phenol	1.7×10^5	$< 1 \times 10^3$	5×10^5	8.4×10^5
Acetanilide	3×10^3	$< 1 \times 10^2$	7×10^3	13×10^3
Benzoic acid	0.0019	0.0081	0.00026	0.020
Ethyl benzoate	0.0026	0.0079	0.0009	0.022

electron density compared with benzene, remember that this relates only to *ground state* structures and stabilities and that the ground state is identical for substitution at *ortho*, *meta*, or *para* positions. The transition states for attack at different positions may, however, differ significantly; it is there that we must seek rationalizations for observed results.

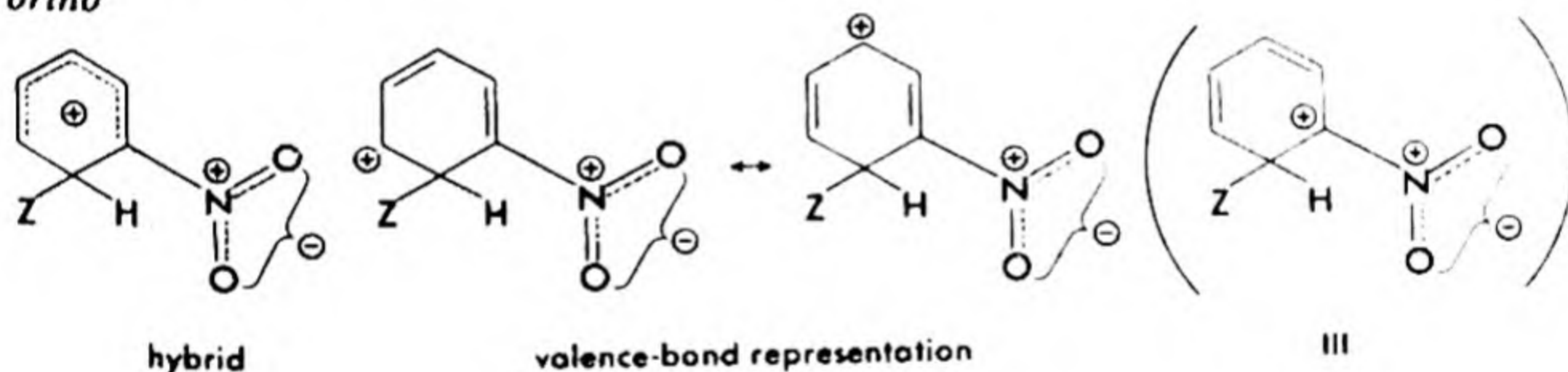
Let us first consider, as an example of a *meta* directing group, the resonance structures of the intermediates resulting from addition of Z^+ at the *ortho*, *meta*, and *para* positions on nitrobenzene and compare these with that for benzene.

Addition to benzene:

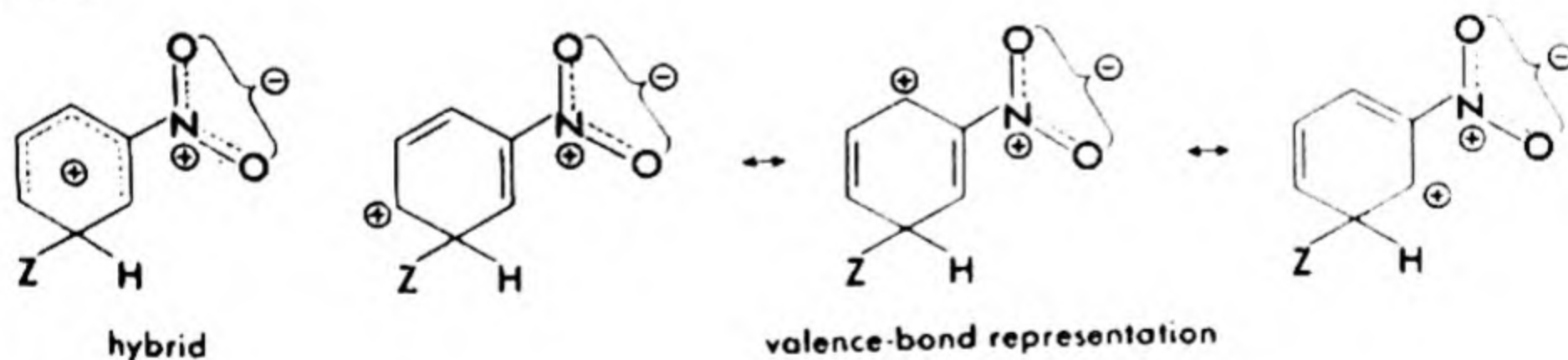


Addition to nitrobenzene:

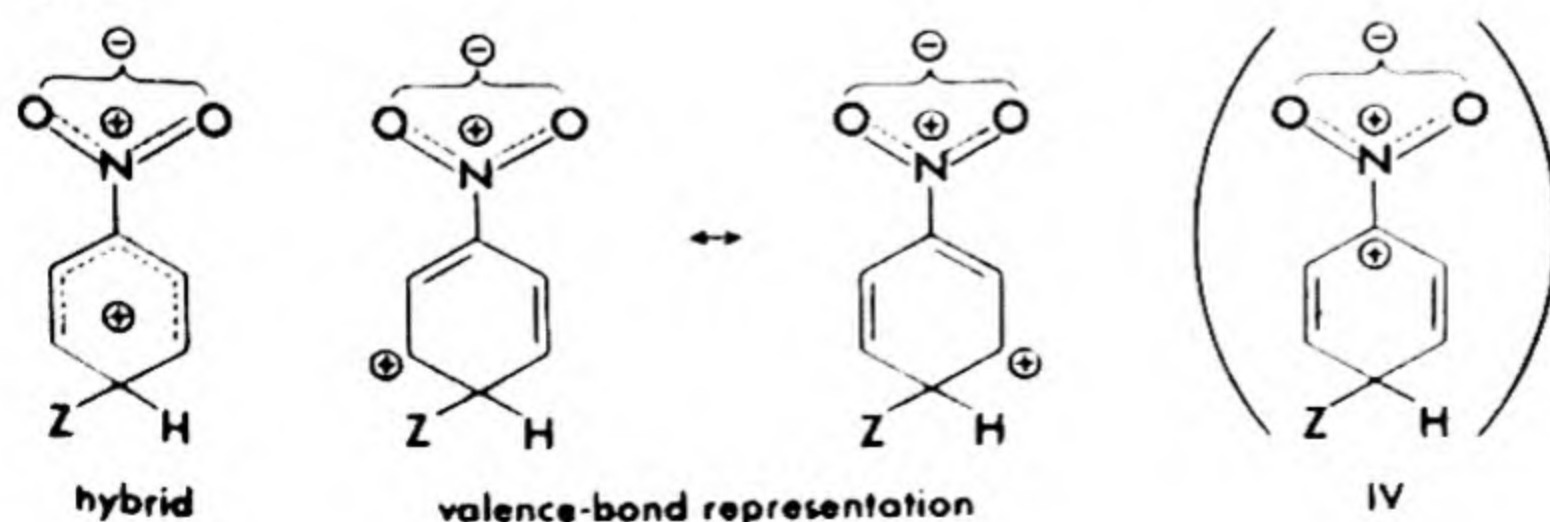
ortho



meta



para



Note that the hybrid structure for benzene has one positive charge, while those for nitrobenzene have not only a similar positive ring charge but also a positive charge on the nitrogen atom attached to the ring. From simple electrostatics it is clear that all of the intermediates (and the corresponding transition states) will then be *less* stable than that for benzene. As nitrobenzene has *more* resonance energy than benzene, the free energy of activation for substitution in *any* position of nitrobenzene is considerably greater than that for benzene. If we now consider the valence-bond structures III and IV, we see that these are very high-energy structures (two positive charges are on adjacent atoms, with high electrostatic repulsion). These structures are assumed to make little contribution to the hybrids. The *meta* intermediate has no structures with similar charges on adjacent atoms; therefore, its transition state is the most stable. Thus, *meta*-substitution is preferred over *ortho* and *para*. This argument is summarized in the energy diagrams in Fig. 16-5.

Similar results will obtain whenever there is a positive charge on the atom attached to the ring. The positive charge may be a formal charge, as in $-\text{NH}_3^+$, $-\text{NR}_3^+$, $-\text{NO}_2$, $-\text{SO}_2\text{OH}$, $-\text{SO}_2\text{OR}$, $-\text{SO}_2\text{R}$, or one that is present because of bond dipoles, as in $-\text{C}(=\text{O})\text{H}$, $-\text{C}(=\text{O})\text{R}$, $-\text{C}(=\text{O})\text{OH}$, $-\text{C}(=\text{O})\text{OR}$, $-\text{C}\equiv\text{N}$, $-\text{CCl}_3$, and $-\text{CF}_3$.

Next let us consider, as an example of an *ortho-para* directing group, the methoxy group of anisole. Again, as described above, anisole is highly

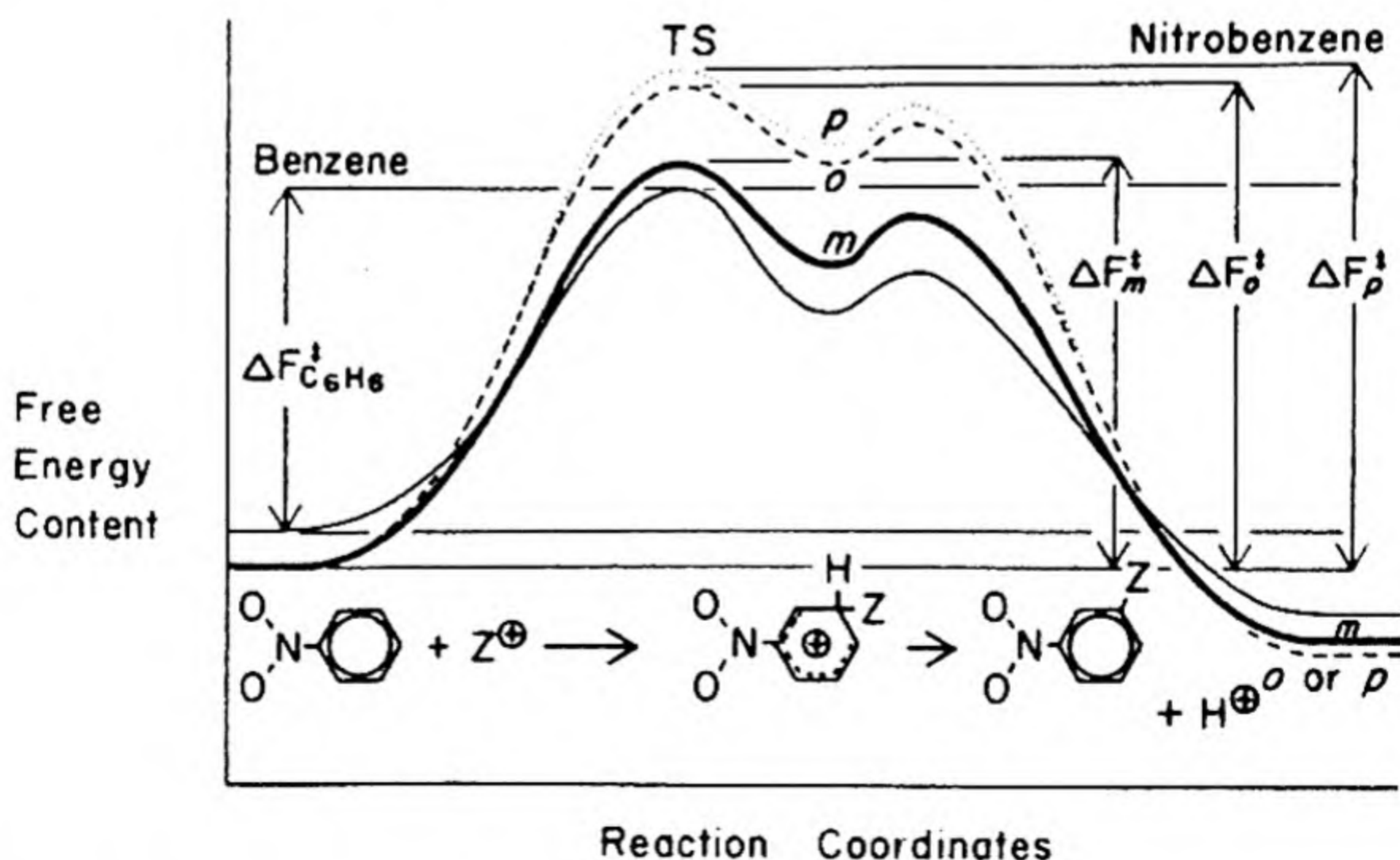
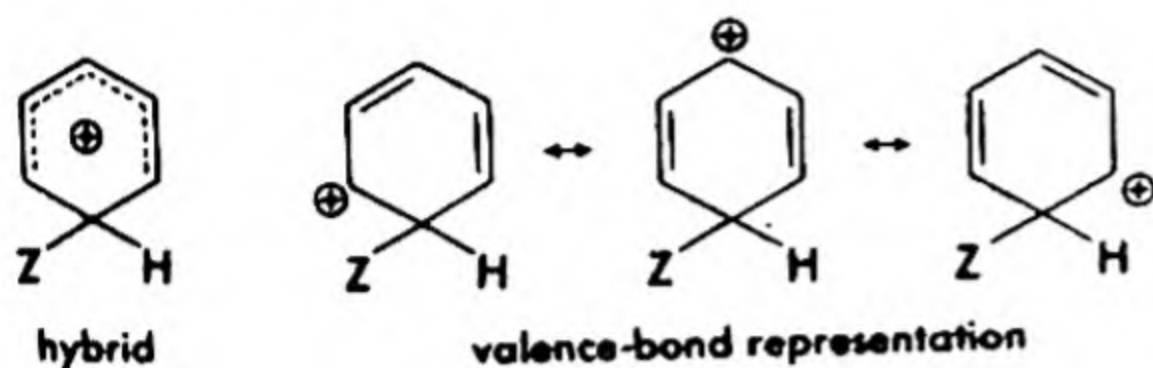


Fig. 16-5. Free Energy Diagrams For Electrophilic Substitution into Benzene and Nitrobenzene.

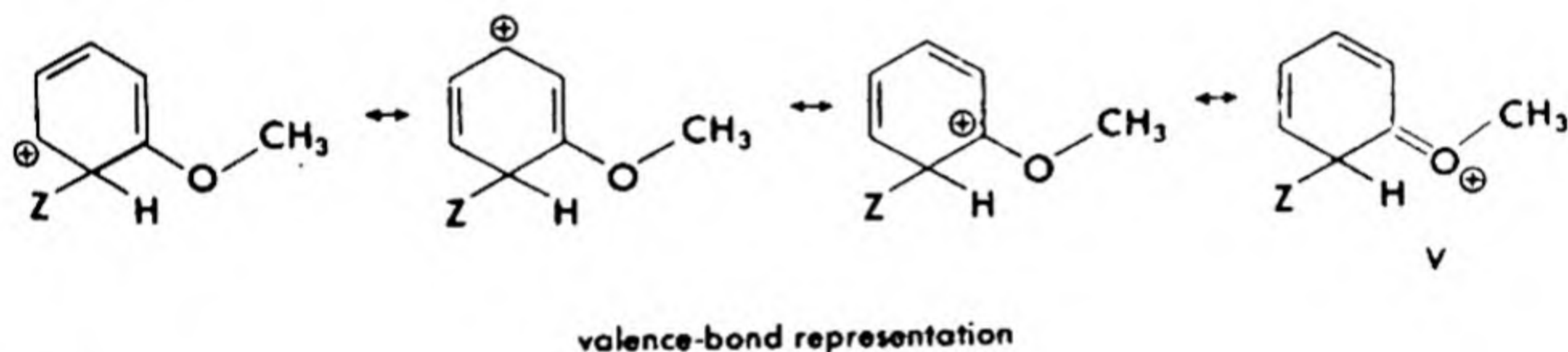
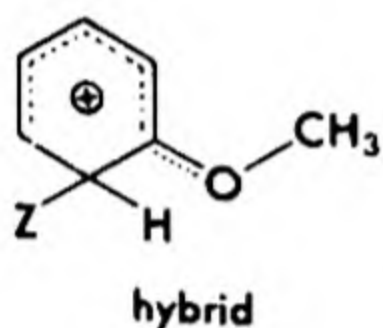
resonance-stabilized in the ground state, so that we must look into the transition states for the explanation of its high reactivity and its *ortho*-*para* orientation. The appropriate canonical structures follow.

Addition to benzene:

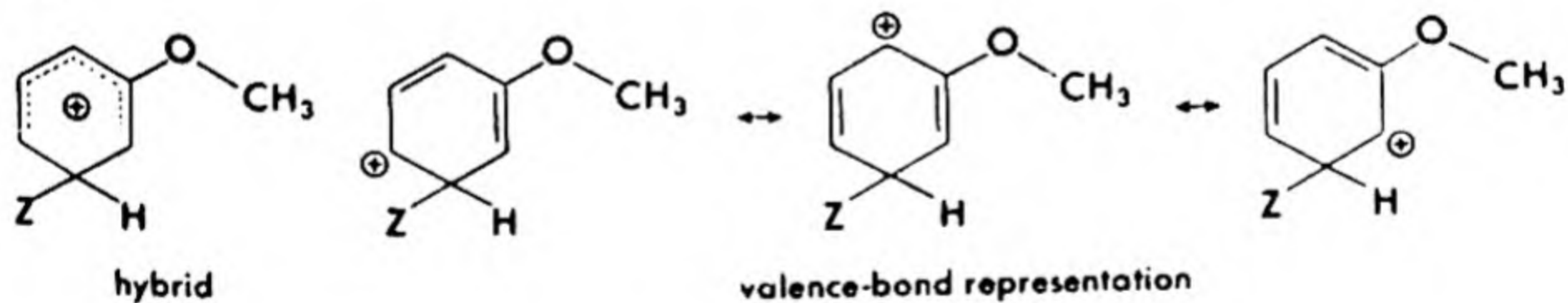


Addition to anisole:

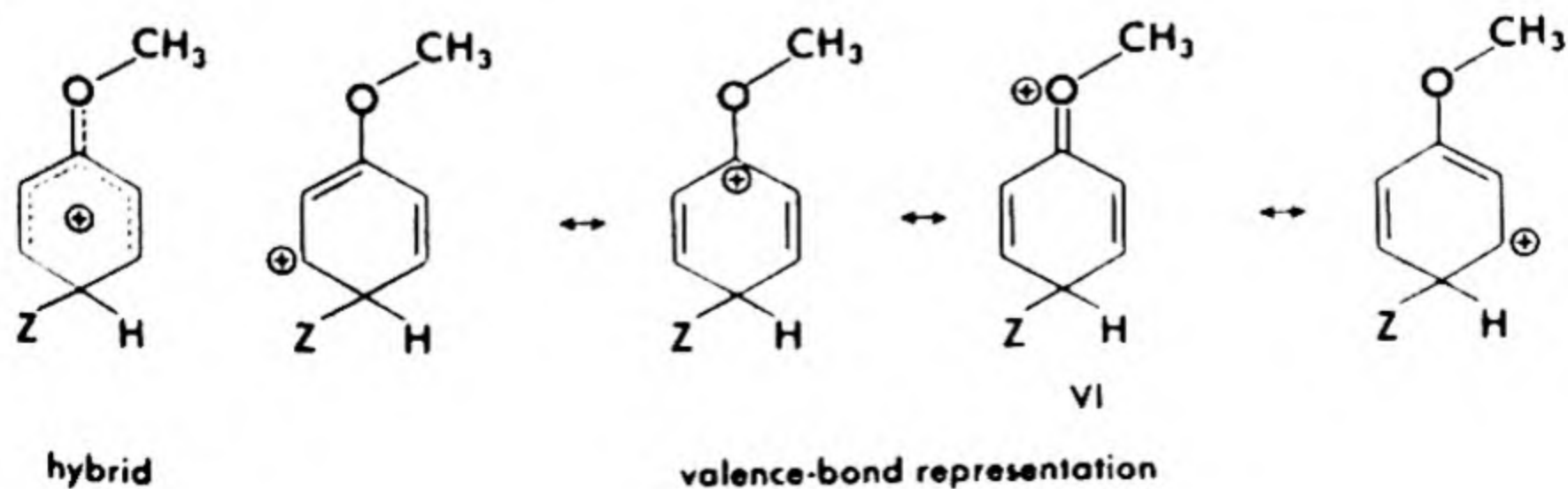
ortho



meta



para



One sees that *all* of the hybrid structures for substitution on anisole are stabilized with respect to that for benzene when one recalls that dipole moment data teach that oxygen donates electrons to the ring even when no charge is present. This donation is increased when an attractive positive charge is present; therefore the substitution rate is increased at *all* positions relative to benzene. However, one notes that for *ortho* and *para* substitution intermediates, but not for *meta*, there is an additional resonance structure, labeled V (for *ortho*) and VI (for *para*). These are especially stable, as each atom has an octet of electrons. The delocalization energies for these hybrids are, therefore, substantially higher, and the ΔF^\ddagger values substantially *lower*, than the corresponding values for the *meta*. Hence, *ortho* and *para* attacks occur significantly faster than *meta* attack. This argument is summarized in the energy diagram in Fig. 16-6.

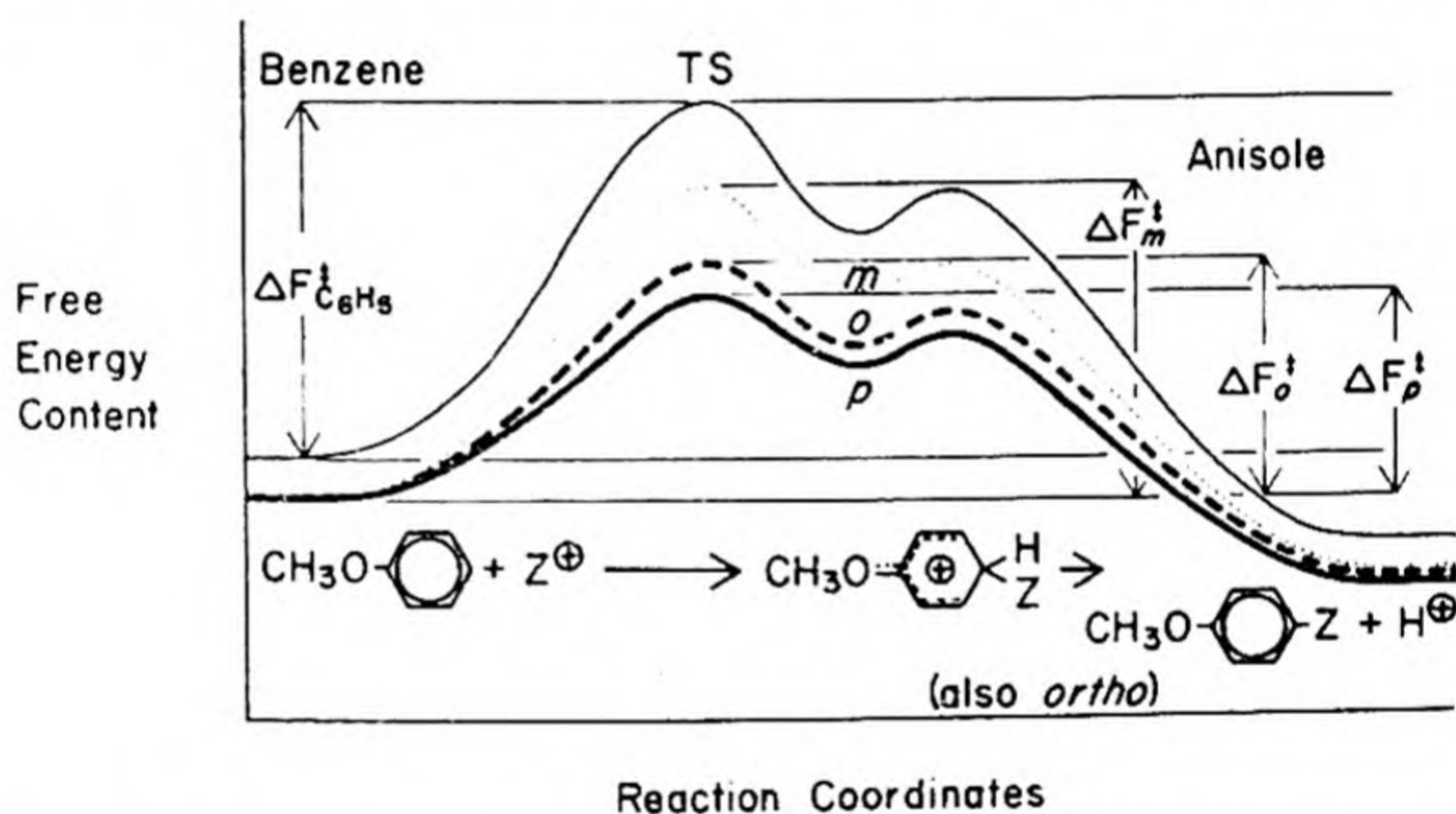


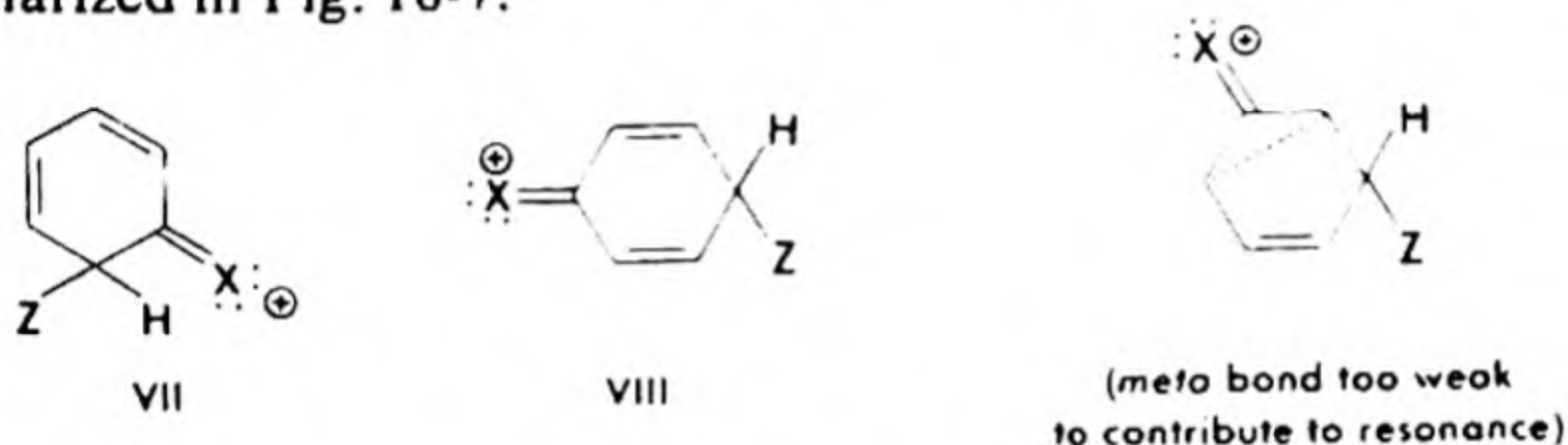
Fig. 16-6. Free Energy Diagrams for Electrophilic Substitution into Benzene and Anisole.

Similar results will obtain whenever the atom or group attached to the ring donates unshared or π electrons readily. Such groups include $-\ddot{\text{O}}^-$, $-\ddot{\text{N}}\text{H}_2$, $-\ddot{\text{N}}\text{R}_2$, $-\ddot{\text{O}}:\text{R}$, $-\ddot{\text{O}}:\text{H}$, $-\ddot{\text{O}}\text{COR}$, $-\ddot{\text{N}}\text{HCOR}$, $-\text{Ar}$, $-\text{CH}=\text{CH}_2$.

We have already noted that alkyl groups can stabilize positive centers on adjacent atoms markedly in our discussions of carbonium ion chemistry (compare relative stabilities of $(\text{CH}_3)_3\text{C}^+$ and CH_3^+), so that alkyl substituents (methyl, ethyl, etc.) fall in the group of *ortho-para* directors and ring activators as well.

There remains one apparent anomaly—the situation of the halobenzenes. All of these compounds react less rapidly than benzene, but in positions *ortho* and *para* to the halogen atom, rather than *meta*. The

situation is clarified by recognition that dipole-moment measurements indicate that the halogens withdraw electrons from the ring. This means that the transition states *for substitution in all positions* have the positive charge due to addition of Z^+ as well as that due to the electron withdrawal by halogen. This situation creates less stable transition states than that for benzene. In addition, involvement of the halogen atoms in resonance stabilizes the *ground states* in respect to benzene. However, consideration of resonance structures for *ortho* and *para* attack reveals a situation similar to the anisole case. Thus, the *ortho* substitution intermediate has the resonance structure VII, and the *para* intermediate the resonance structure VIII. No corresponding resonance structure can be written for the *meta* intermediate, as overlap across meta positions is too weak for bonding. Hence the *ortho* and *para* intermediates have greater resonance stabilization and their transition states are lower in energy. This argument is summarized in Fig. 16-7.



Anilinium salts generally exist in equilibrium with the free amine, which is so much more reactive than the salt that all reaction may occur through the amine even when it accounts for a very small amount of the total material present. However, in some mixtures, for example, concentrated nitric and concentrated sulfuric acids, the acid is strong enough to eliminate substantially all of the free amine. Then the salt reacts and *meta* substitution results. The amino group is so readily oxidized by dilute nitric acid that nitration cannot usually be carried out successfully under these conditions.

B. Steric Factors in Orientation: the *Ortho/Para* Ratio

In *ortho-para* directing systems, *para* substitution generally occurs to a much greater extent than the statistical expectation, which is $\frac{2}{3}$ *ortho* and $\frac{1}{3}$ *para*. A large share of this discrepancy is believed to be due to a steric effect, as the transition state for *ortho* substitution may involve serious steric interaction between the entering Z^+ group and any group *ortho* to it. This steric interaction is destabilizing, hence decreases the rate of *ortho* substitution. This effect increases as the size of the Z group and the size of the group already present increase. Thus, for nitration (with NO_2^+), the per cent of *ortho* isomer in the *ortho/para* mixture decreases from 61 to 48, 32 and 18%, respectively, as one goes down the series $\text{C}_6\text{H}_5\text{—CH}_3$,

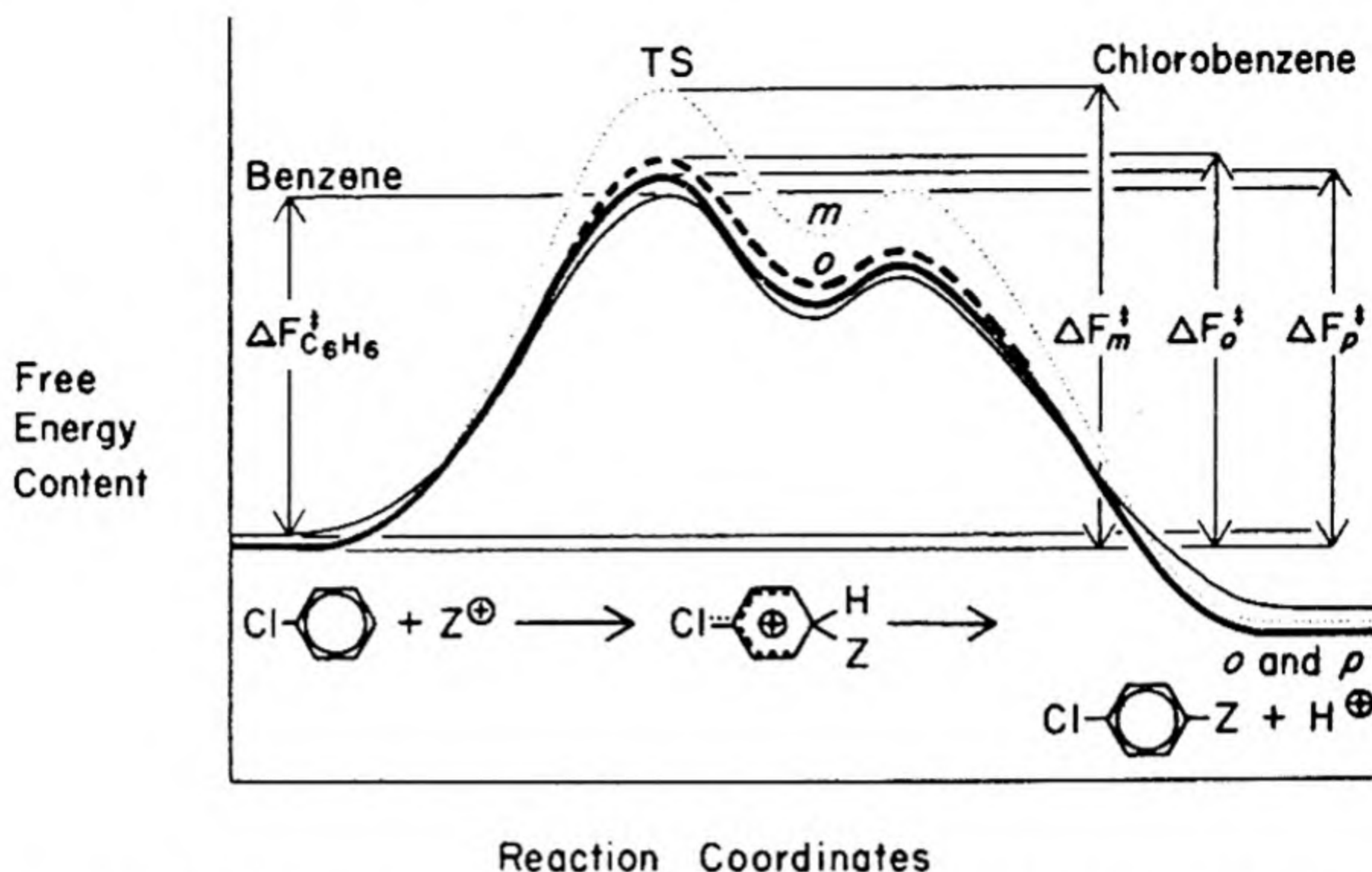


Fig. 16-7. Free Energy Diagram for Electrophilic Substitution into Benzene and Chlorobenzene.

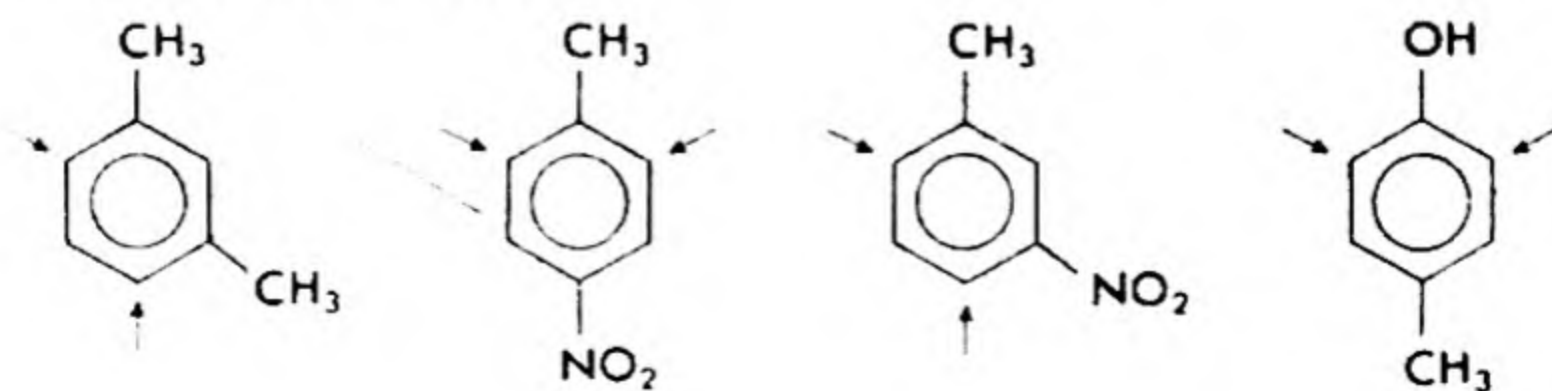
$\text{C}_6\text{H}_5\text{—CH}_2\text{CH}_3$, $\text{C}_6\text{H}_5\text{—CH}(\text{CH}_3)_2$ and $\text{C}_6\text{H}_5\text{—C}(\text{CH}_3)_3$. (The *ortho/para* ratio may be influenced to some degree by electrical forces as well.)

C. Orientation with Several Groups Present

When two or more groups are already present on a ring, the principles described above still apply. When both groups direct to the same position or positions and the groups are both rate-enhancing, the groups are additive in their effects in increasing rates; when both are deactivating, the rate is decreased by the additive effects of both groups. For this reason, nitrations beyond the second stage in aromatic substrates without activating groups is impracticable. If one group is activating and another deactivating, the reactivity lies between that of the two monosubstituted compounds.

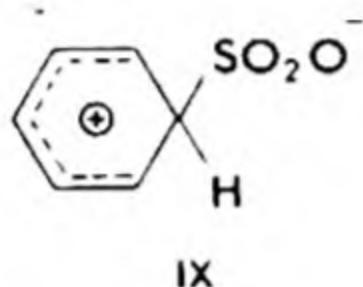
When two groups have opposing directive influences, the group which activates the ring more always has the greater effect; the one which deactivates it more has the lesser effect.

Steric factors become very important when two groups are *meta* to each other. The position between them is highly hindered, hence less likely to react than other activated positions in the molecule. Some examples of preferred orientation follow.



D. Reversibility in Aromatic Substitution

Some of the reactions described in this chapter, particularly sulfonation and nitration at high acid strengths, and Friedel-Crafts alkylations, are reversible. The reverse substitutions proceed through the same transition states and intermediates as the forward reaction but in reverse order, with the result that the group is replaced by hydrogen. The equilibrium position, when attained, depends upon the conditions of the experiment. Thus, treatment of benzene with cold disulfuric acid gives benzenesulfonic acid; treatment of benzenesulfonic acid with 50% sulfuric acid at 150° regenerates benzene. The intermediate for both reactions is probably IX. The outcome of the reaction depends on the concentration of water in the system (eq. 52).



A further consequence of reversibility arises when reactions are conducted for long enough periods of time or at high enough temperatures to establish equilibrium. The orientation rules predict the result of *kinetic*

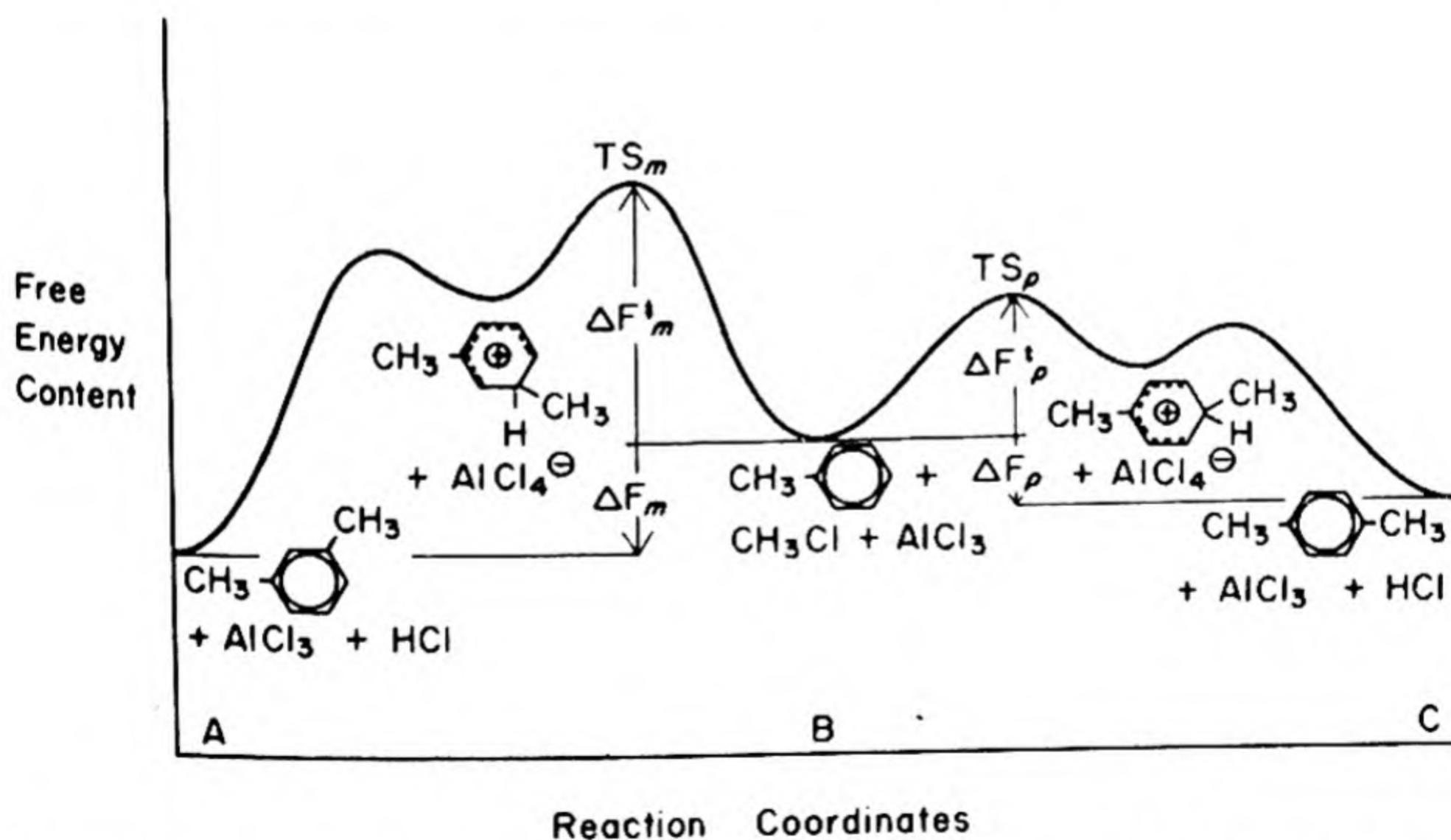


Fig. 16-8. Energy Diagrams for Methylation of Toluene. (A) Principal final products (after equilibrium is established). (B) Reactants, (C) Principal initial products. Reaction goes faster to C, through the lower ΔF , but eventually favors A, where $-\Delta F$ is greater (in absolute value).

control, that is, the result when a reaction occurs under essentially irreversible conditions in which reaction rates govern the ratio of products formed. Under reversible conditions, that is, *equilibrium* or *thermodynamic* control, the product composition may be quite different. In fact, Friedel-Crafts alkylations often give *meta*-disubstituted hydrocarbons as the principal product for this reason. A transition-state diagram illustrating such a situation is given in Fig. 16-8.

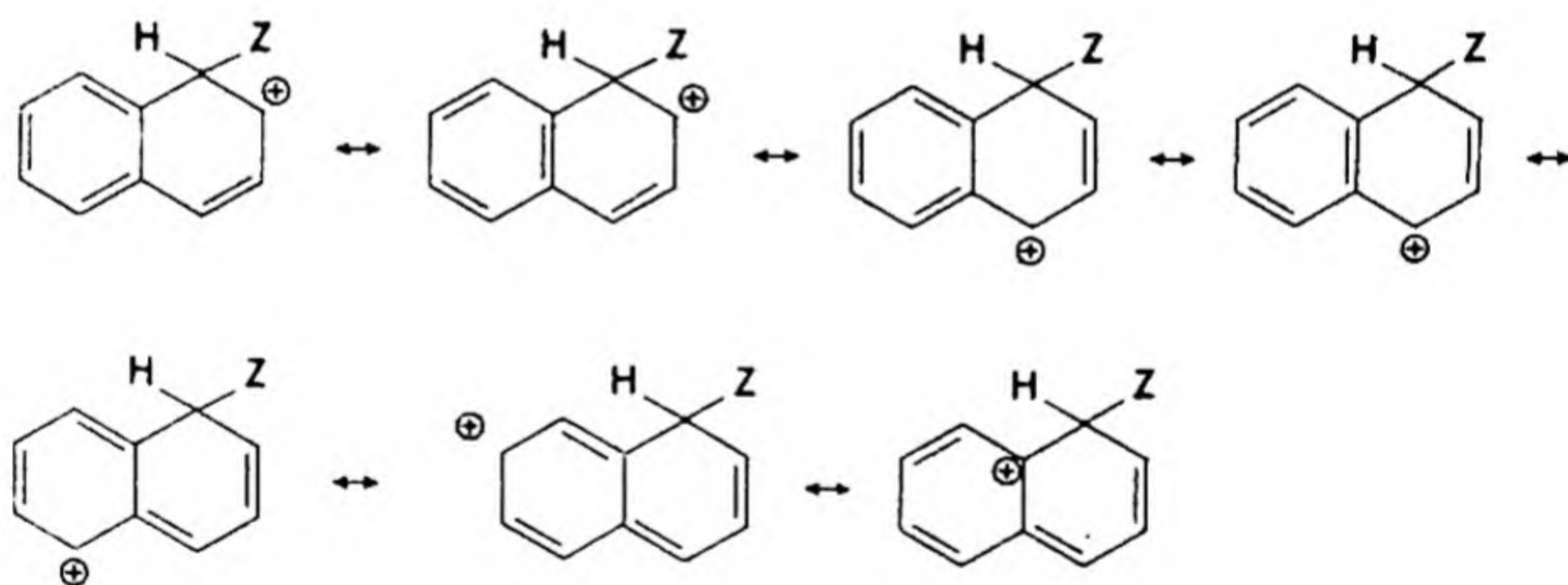
16-5 REPRESENTATIVE REACTIONS

A. Halogenation

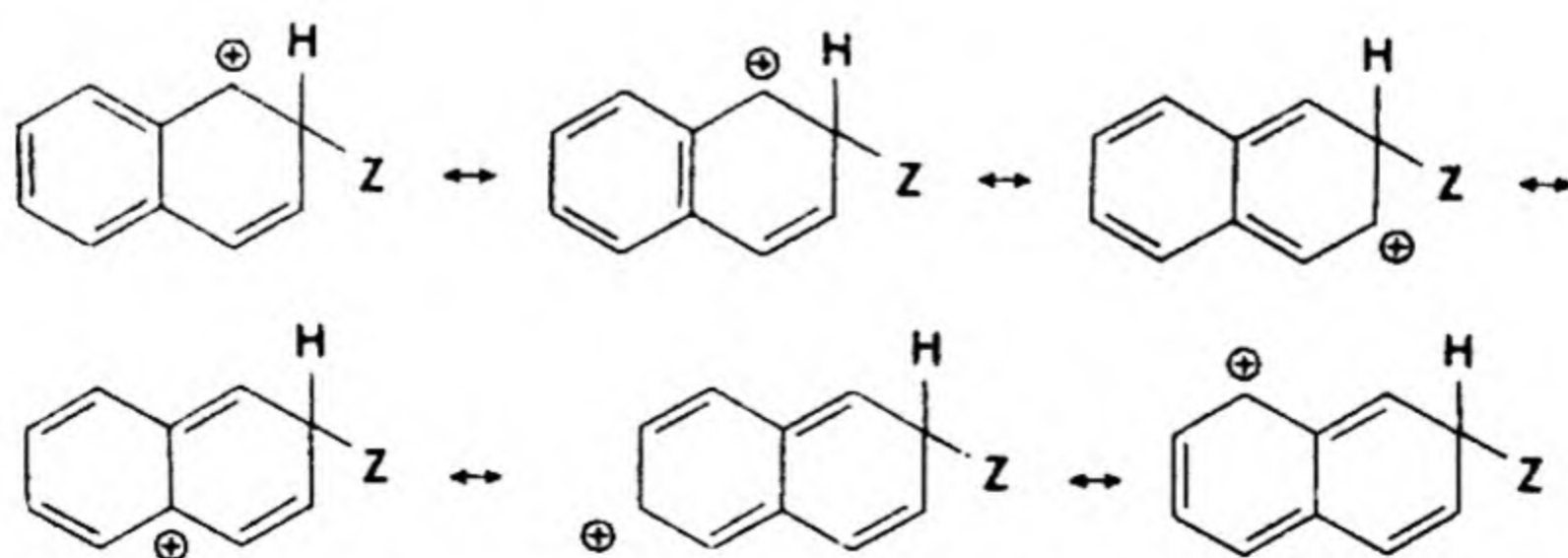
Toluene can be chlorinated either on the ring or on the methyl group depending on whether a carrier or light is used to activate the halogen. The methyl-group directs the chlorine atom to the *ortho* and *para* positions during ring substitution.

Naphthalene is brominated mainly on the alpha position, due to relative stabilities of the α and β transition states. See the sigma complex valence bond structures below. The complex for α -attack has an additional Kekulé canonical structure, which means a greater delocalization of electrons stabilizes the α -complex more than the β -complex.

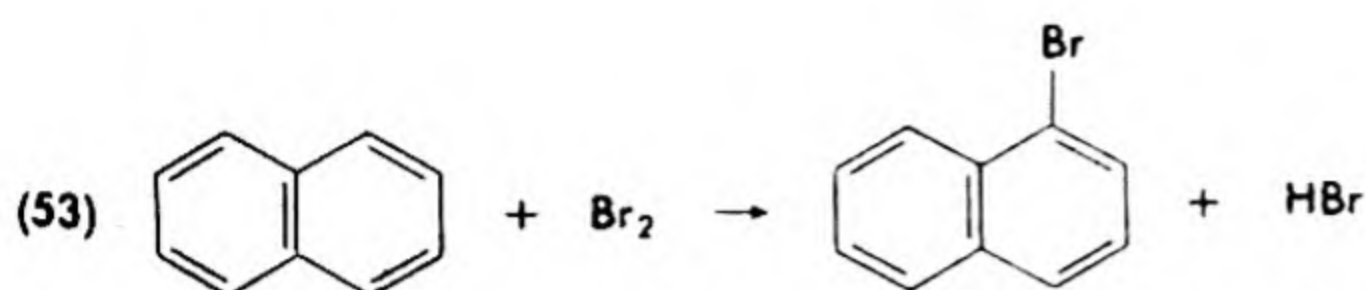
alpha attack:



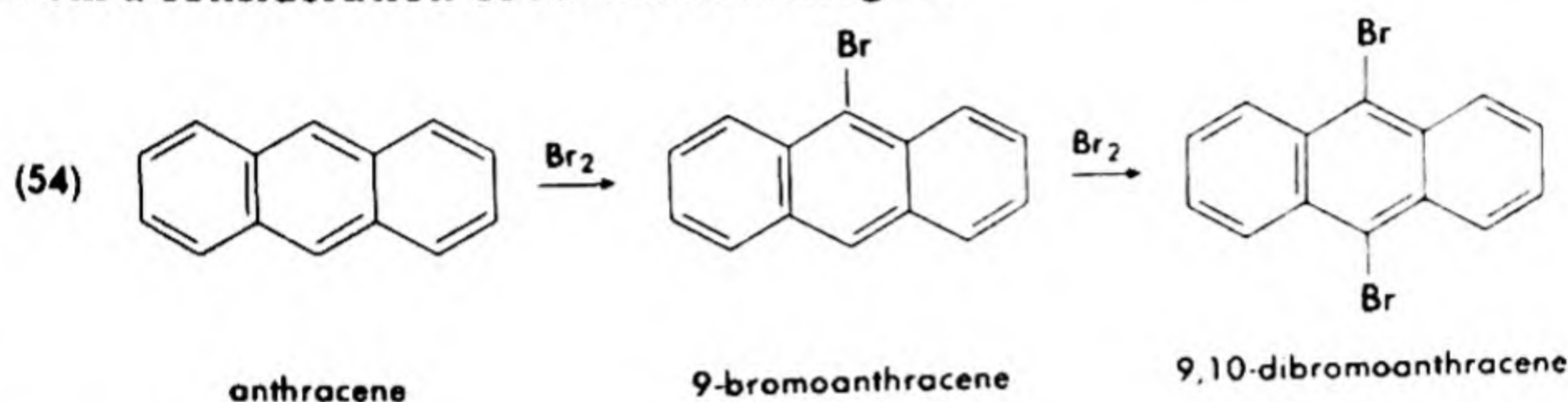
beta attack:



α -Bromonaphthalene can be prepared in 72-75% yield.

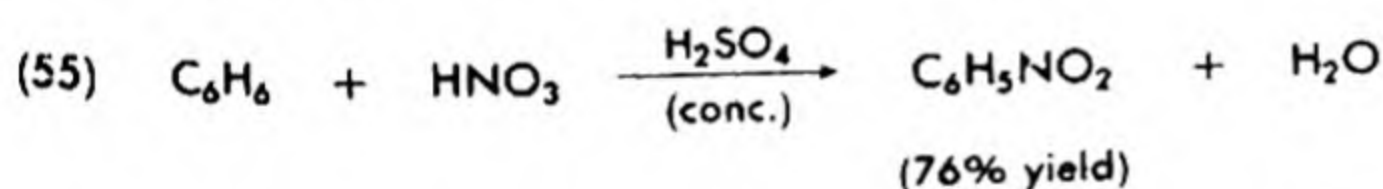


Anthracene is halogenated at the 9 position. The second halogen goes into the 10 position. No catalyst is required. Reactivity of anthracene is always greatest at the *meso* (9 and 10) positions. This can be understood from a consideration of resonance energies.

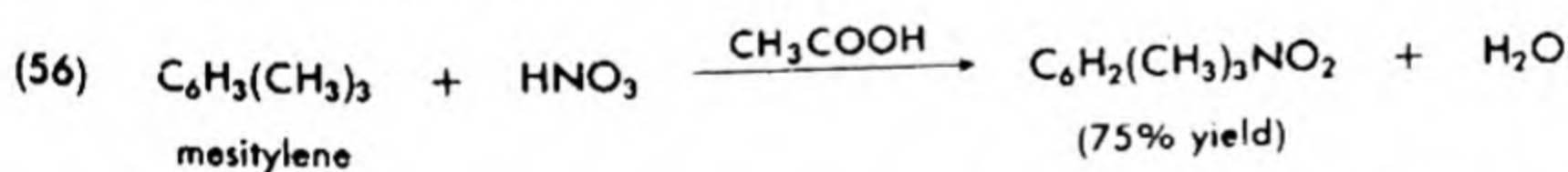


B. Nitration

Nitration of arenes is much easier than nitration of alkanes and is carried out with success in either laboratory or industrial plant. The preparation of nitrobenzene is a classic example.



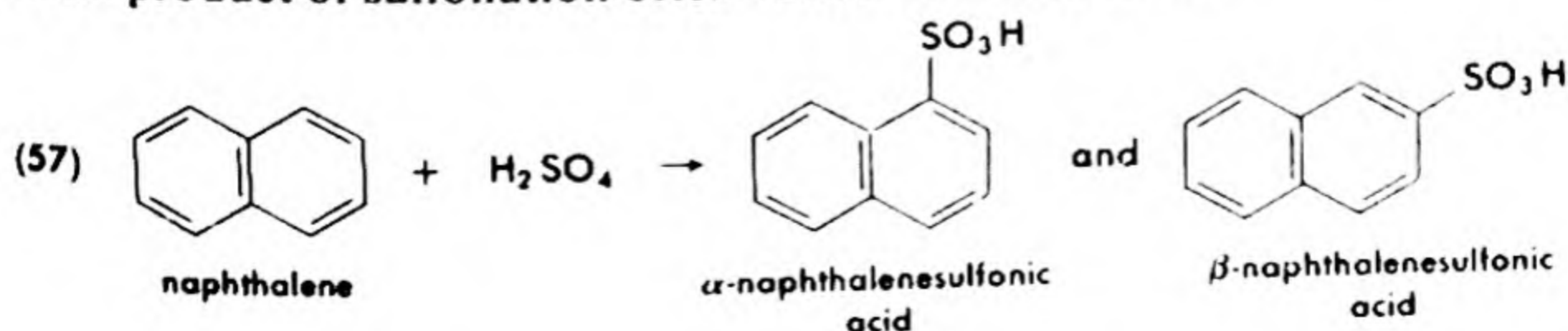
More active hydrocarbons, such as mesitylene, can be nitrated using glacial acetic acid instead of sulfuric acid as catalyst.



Nitration of nitrobenzene is difficult, and of dinitrobenzene impracticable. However, a methyl group activates the aromatic ring sufficiently to make three-stage nitration of toluene commercially feasible. The resulting TNT is an important high explosive.

C. Sulfonation

All arenes can be sulfonated; however, the reaction is not as simple and direct as might appear. Sulfonation is a reversible reaction; hence, the main product of sulfonation often varies with conditions.



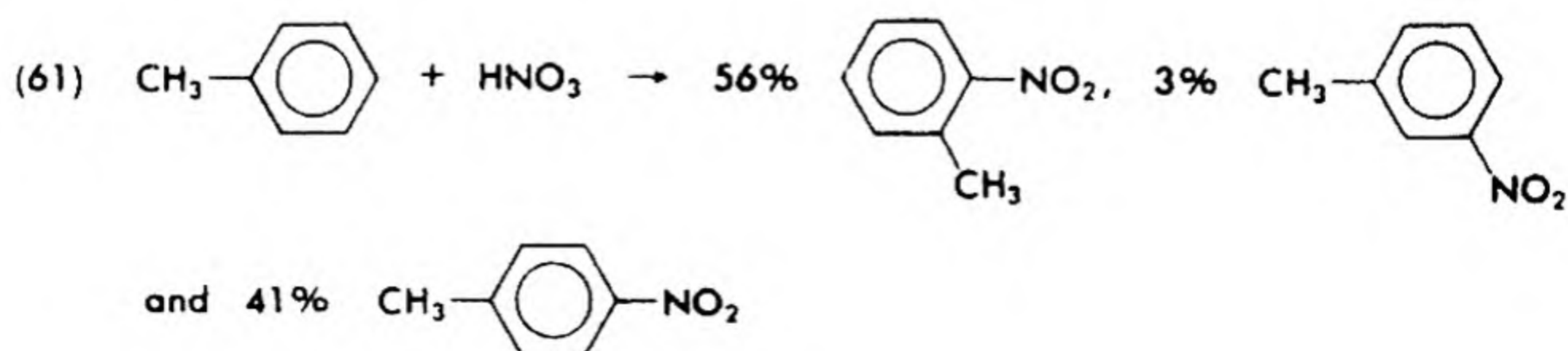
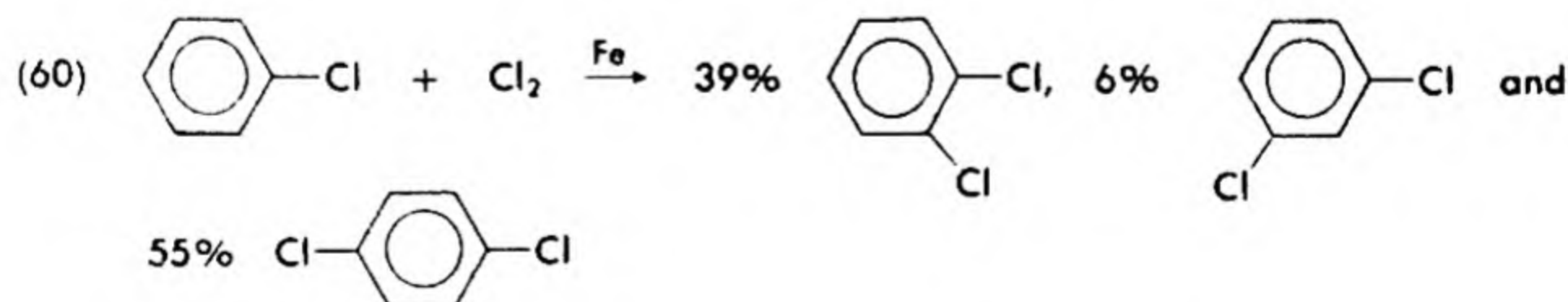
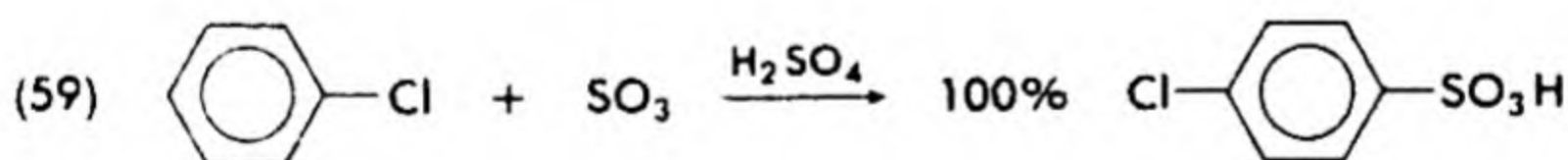
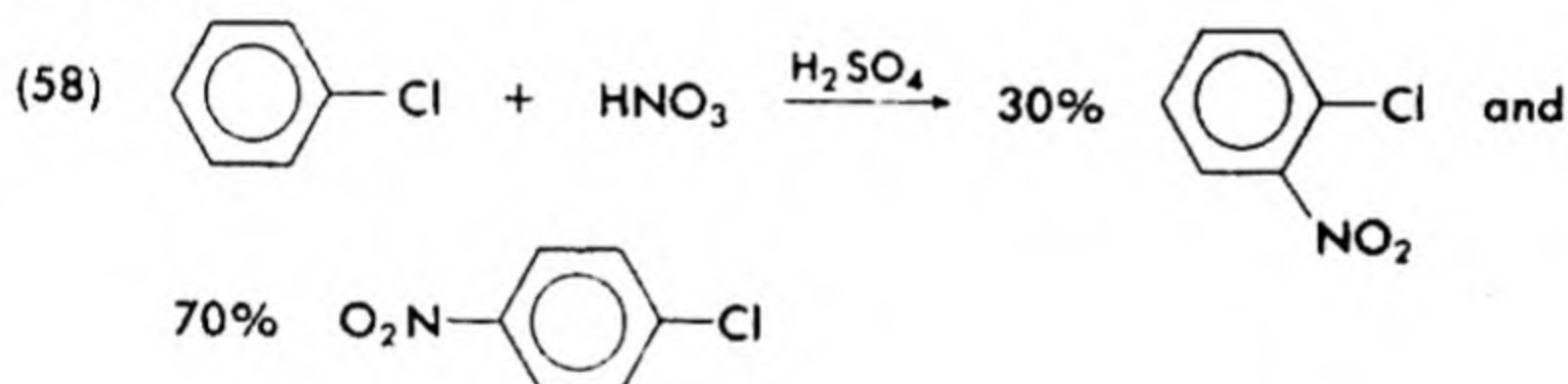
Sulfonation of naphthalene at 80°, under which conditions the position of substitution is determined by kinetic control, gives mainly α -naphthalenesulfonic acid. However, at 160° under conditions where the reaction is thermodynamically controlled, the ratio of monosulfonation products is 15% alpha to 85% beta. In the α -isomer the sulfo group has compressional strain against the peri-(8) hydrogen atom. This is not found in the β -isomer, which is, therefore, more stable.

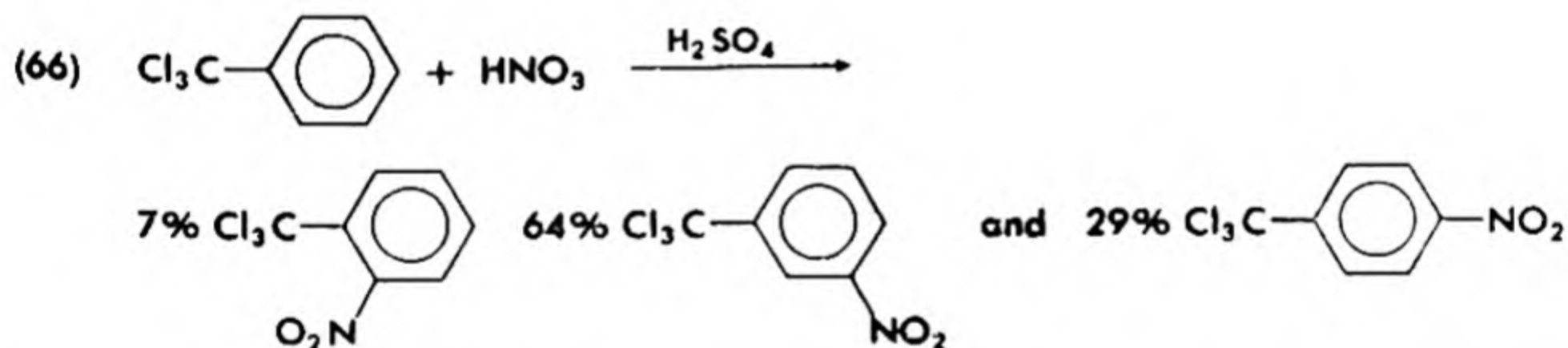
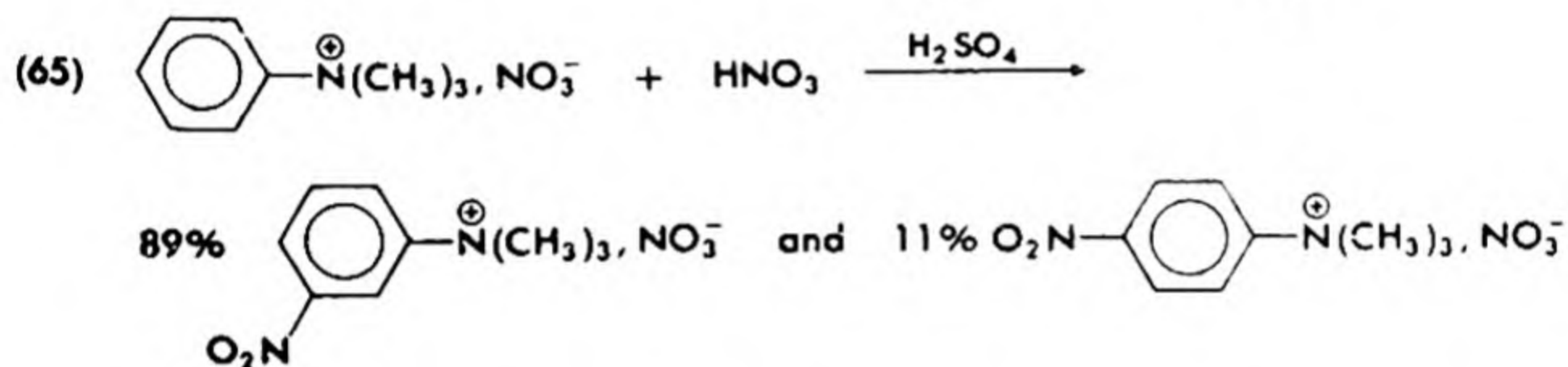
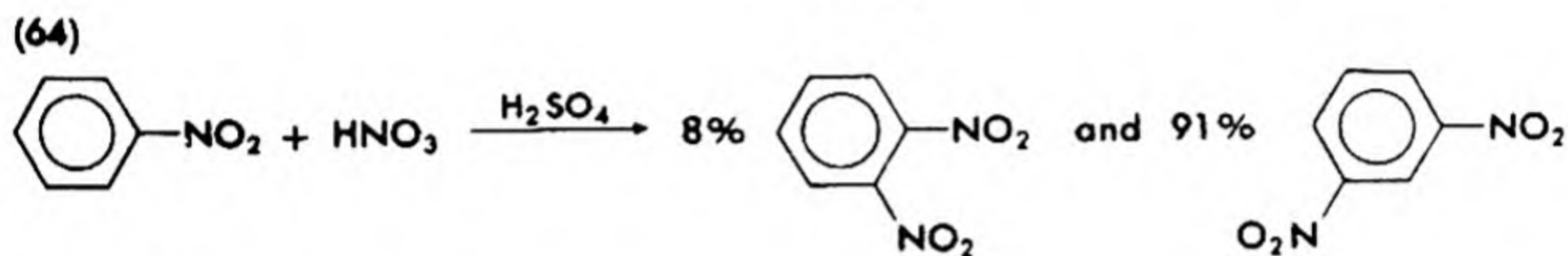
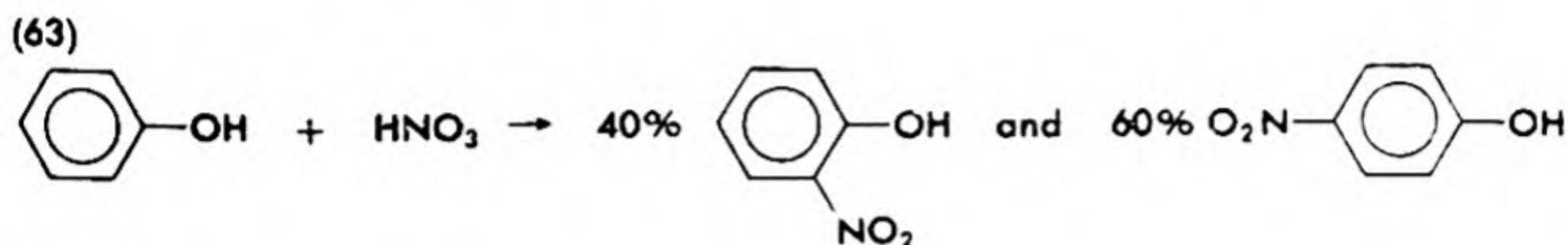
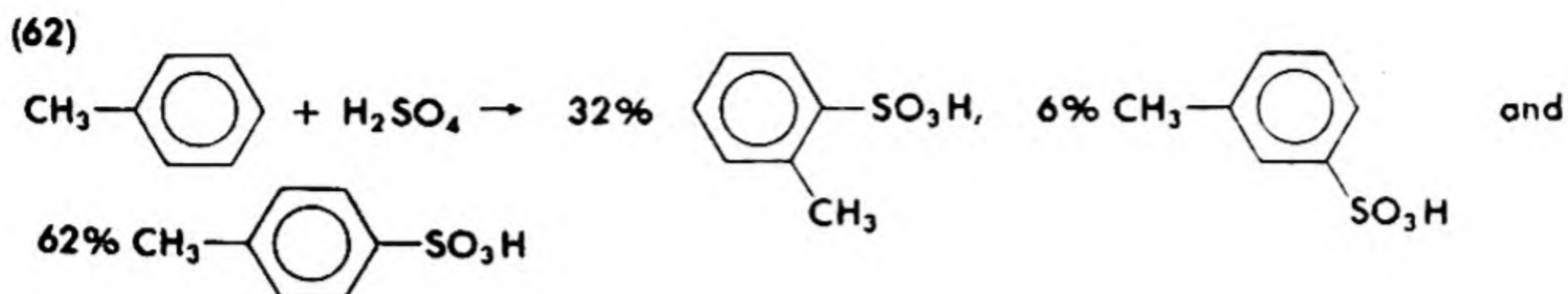
Chlorosulfonic acid is used to prepare arenesulfonyl halides directly from the hydrocarbons.

D. Typical Reactions Demonstrating Orienting Effects

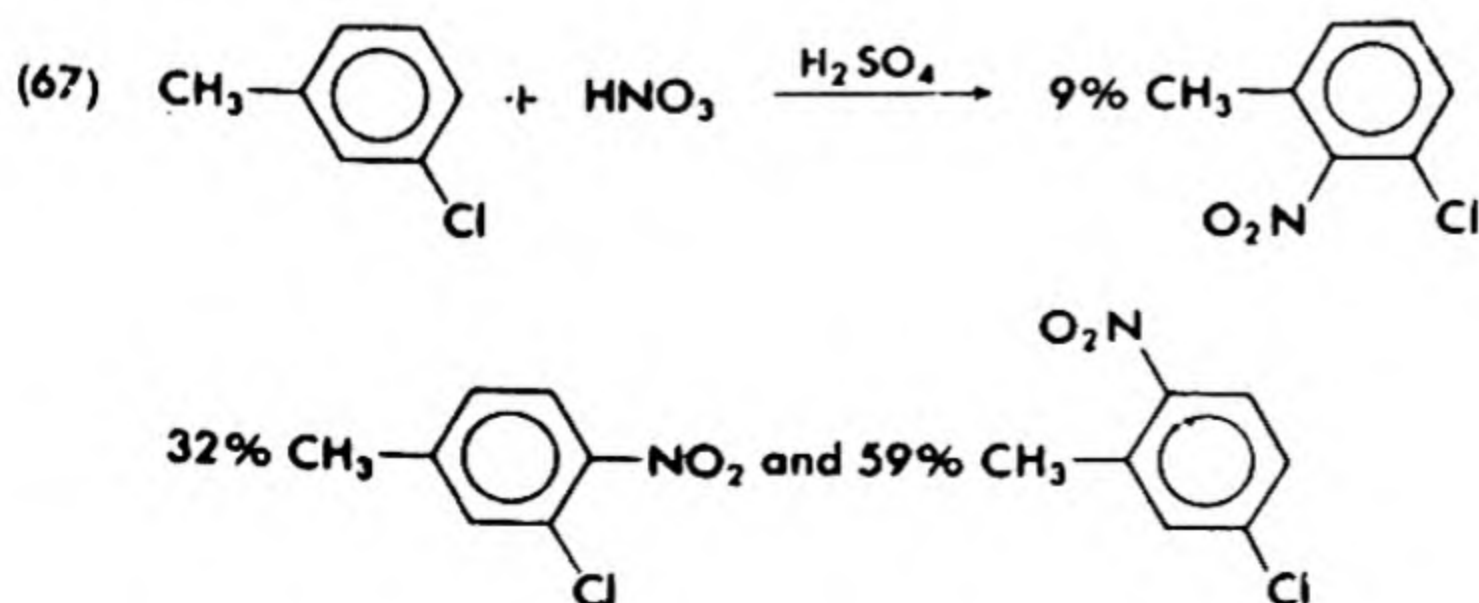
Substitution in aromatic compounds is one of the most thoroughly investigated areas of organic chemistry. From the host of available examples only a few can be included here. For somewhat more extensive treatment of the subject, any of the supplementary readings listed at the end of this chapter may be consulted.

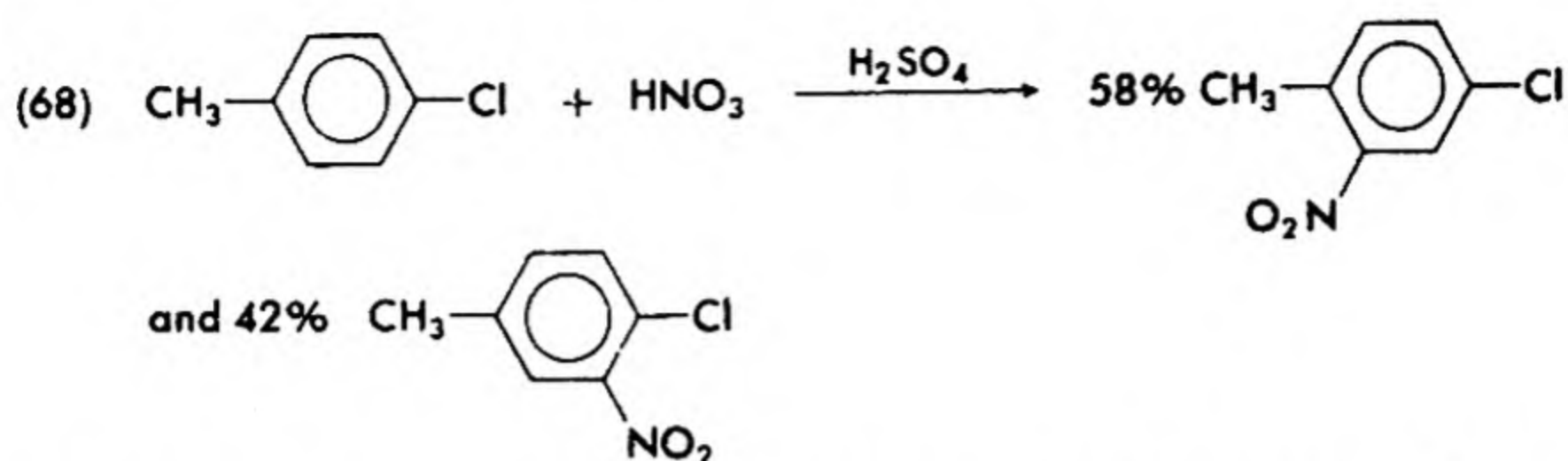
In the following outlines of selected reactions, the directing effects are seen to be in agreement with predictions made earlier, including the greater than statistical ratio of *para* to *ortho* substitution with *o,p*-directing groups in the ring. The percentages given are product ratios, not yields.





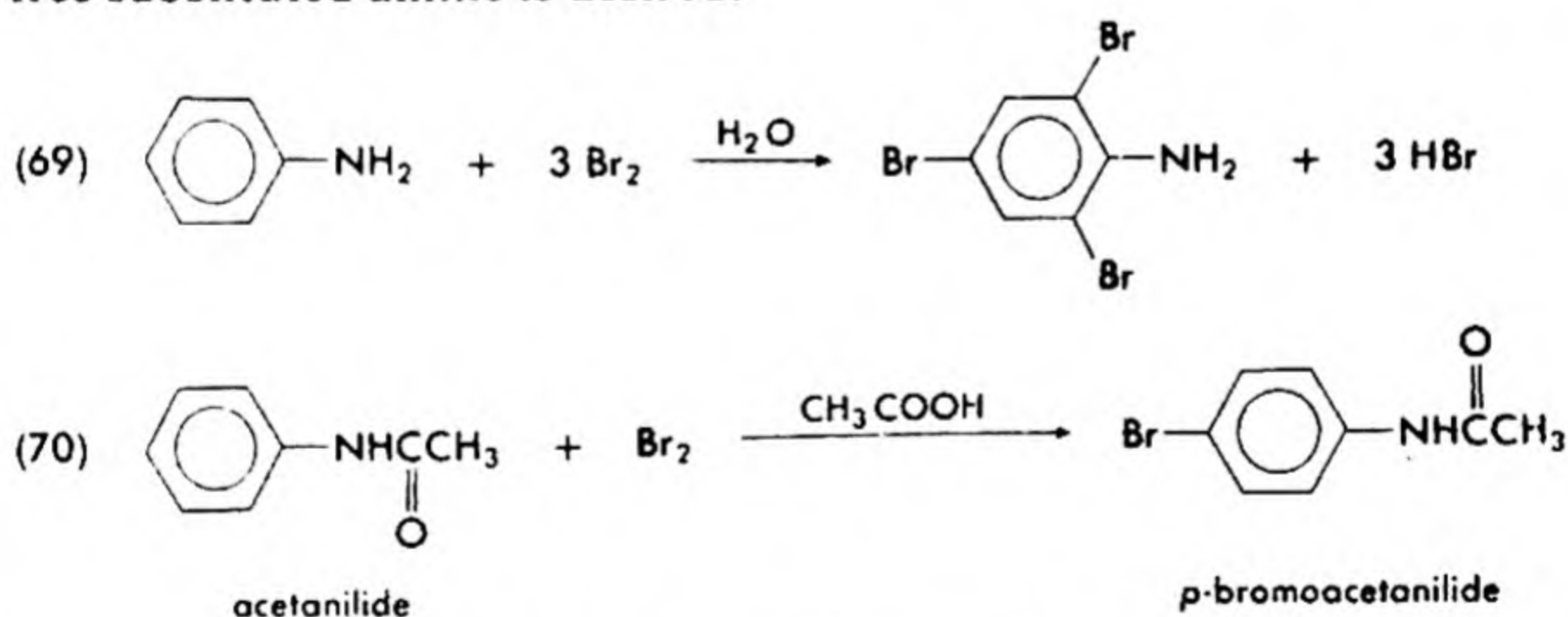
Electron withdrawal by the three chlorine atoms makes the trichloromethyl group a *meta*-directing group (outline 66). Benzyl chloride and benzal chloride are intermediate between toluene and benzotrichloride in behavior.



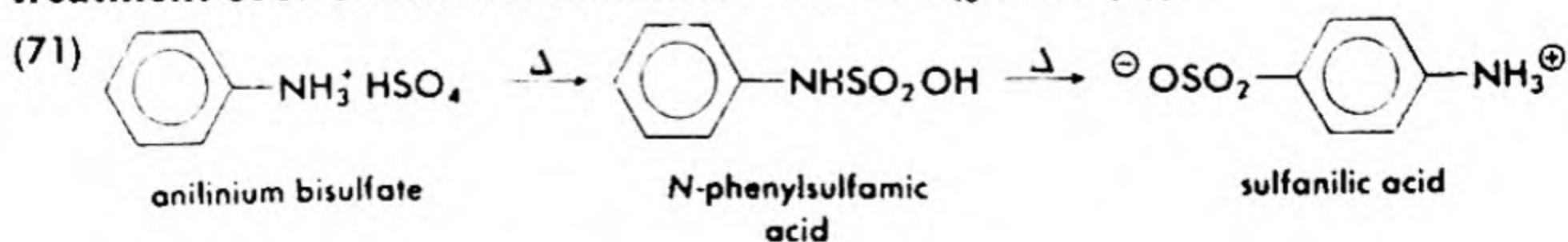


Outline (67) illustrates the effect of steric hindrance tending to block the nitro group from entering between the methyl group and the chlorine atom.

Advantage is taken of the somewhat diminished reactivity in acylated derivatives of amines to decrease polysubstitution. Acylation also prevents oxidation of the nitrogen atom and salt formation with consequent *meta* substitution. This use of acylation to decrease side reactions of amines during substitution is called *protection of the amino group*. The difference in behavior between the aryl amine and the aryl amide is illustrated by the results of bromination of aniline and acetanilide. In spite of the fact that the reaction between aniline and bromine water is heterogeneous (immiscible layers), the amine is tribrominated. Homogeneous reaction with acetanilide in glacial acetic acid serves to brominate only one position when the amount of bromine added is controlled. The usefulness of acylation to modify the activating effect of the amino group depends on the ready removal of the acetyl group after substitution when the free substituted amine is desired.

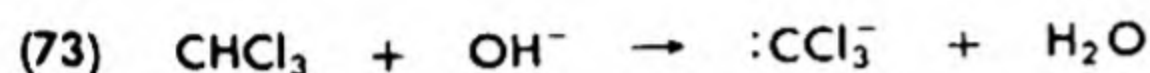
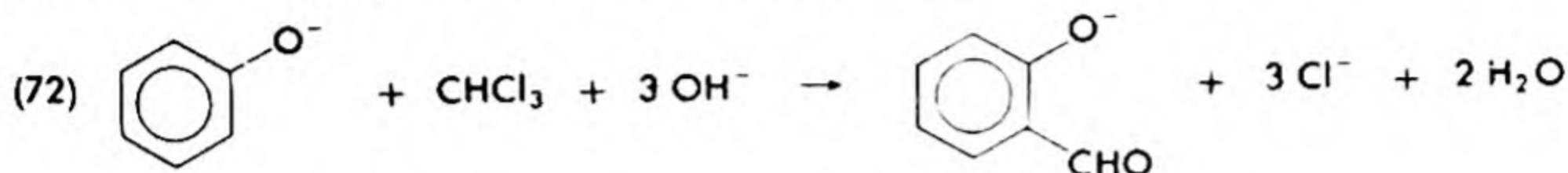


Surprisingly, unprotected aromatic amines can be sulfonated by heating their sulfate salts. This, however, involves the intermediacy of the aryl sulfamic acid and is a typical nitrogen-to-*para* rearrangement observed on treatment of *N*-substituted anilines with acid (§25-4B(1)).

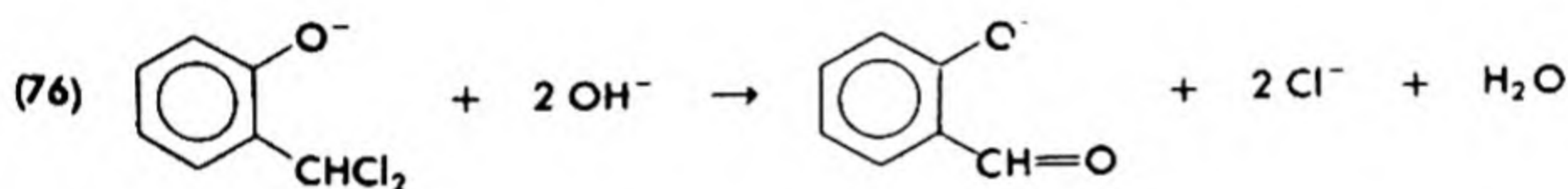
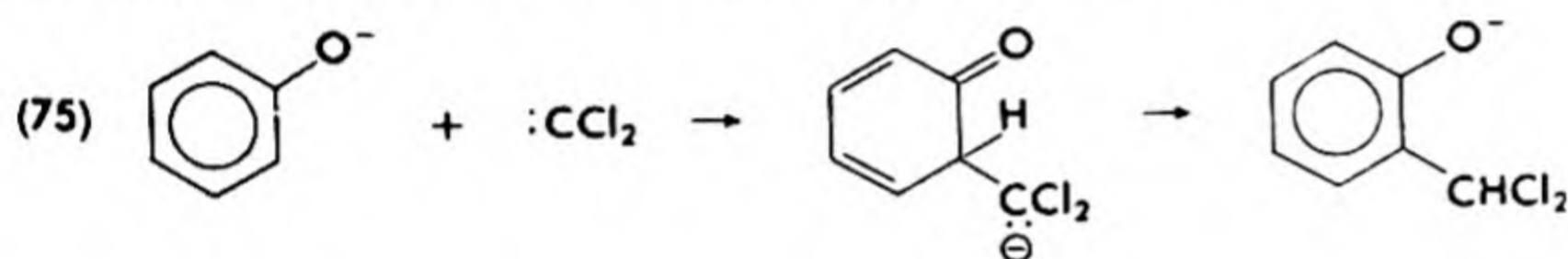


E. Reimer-Tiemann Reaction

When sodium phenoxide is treated with chloroform and a base, salicylaldehyde results (eq. 72). This reaction involves the formation of dichlorocarbene (eqs. 73 and 74), electrophilic attack on the phenoxide ion



by dichlorocarbene, followed by rearrangements and hydrolysis (eqs. 75 and 76). This is called the *Reimer-Tiemann reaction*.

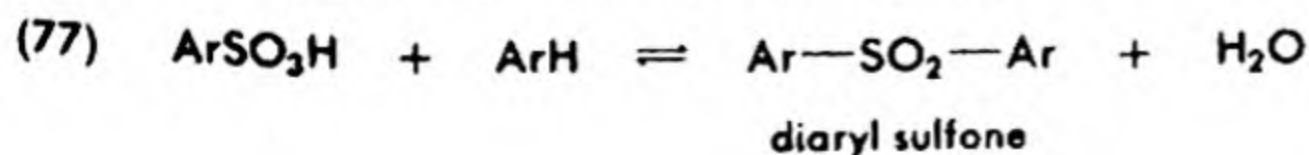


16-6 SIDE REACTIONS

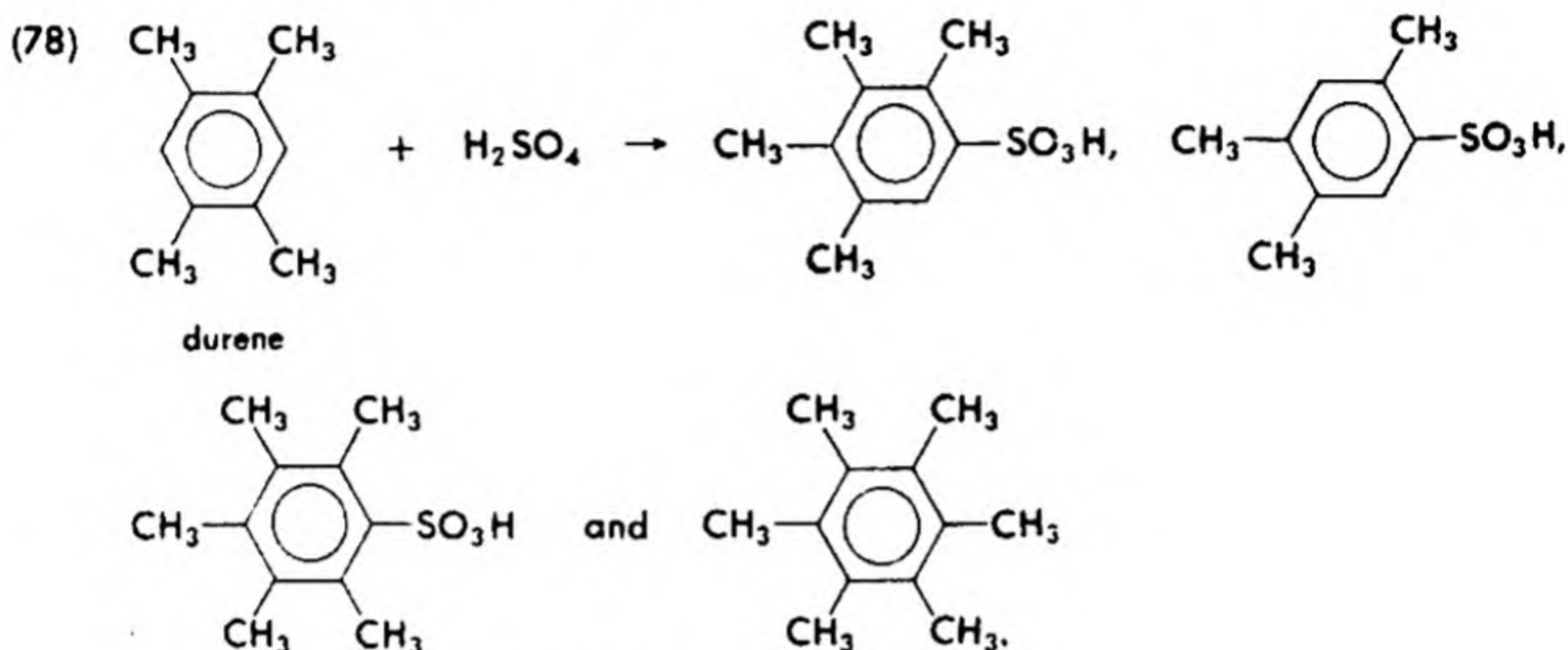
In all substitution reactions in substituted arenes, isomer formation is a factor. Although orientation effects dictate the major products obtained, they seldom forbid other orientations completely. Thus, mixtures of isomers are obtained which require separation. In the absence of strong intramolecular chelation, *para*-disubstituted isomers almost invariably have the highest melting points and lowest solubilities and are generally most readily purified.

Polysubstitution is also quite possible, especially with activating groups. This is especially true in halogenations. The nitro group and sulfo group so decrease the reactivity of an aryl radical that this is not as detrimental to yields of mononitro or monosulfo compounds as polyhalogenation is to yields of monohalo compounds.

The similarity between sulfonic acids and sulfuric acid is responsible for another kind of side reaction in sulfonations. The sulfonic acid is also a sulfonating agent and can react with the hydrocarbon to form sulfones.



A surprising type of side reaction occurs in the sulfonation of polyalkylbenzenes, such as durene, which have four or more alkyl groups. Some of the methyl groups in this hydrocarbon migrate on the same molecule, and some even change molecules. This type of reaction has come to be recognized as "normal" for such hydrocarbons and has been called the Jacobsen rearrangement (see §25-4A).



SUPPLEMENTARY READINGS

Berliner, E., "Electrophilic Aromatic Substitution Reactions," *Prog. Phys. Org. Chem.* **2**, 253 (1964).

Gould, C. S., *Mechanism and Structure in Organic Chemistry*, Holt-Dryden, New York, 1959, pp. 412-452.

Hine, J., *Physical Organic Chemistry*, 2nd Ed., McGraw-Hill, New York, 1962, Chapter 16.

Ingold, C. K., *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N.Y., 1953, pp. 223-243, "Electrophilic Aromatic Substitution." (Other examples of interest are discussed through p. 269; however, some of the theoretical discussion in this part may be abstruse enough to detract from the context for any but the most able student at the undergraduate level.)

Mare, de la, P. B. D., and J. H. Ridd, *Aromatic Substitution—Nitration and Halogenation*, Academic Press, New York, 1959.

Smith, L. I., "The Jacobsen Reaction," *Org. React.*, **I**, 370-384, 1942.

QUESTIONS AND PROBLEMS

1. Write a discussion of the sulfonation reaction. Bring out the following points: the nature of sulfonating agents, why they are effective, conditions effective for sulfonation, and side reactions to be expected.

2. Write a discussion of the nitration of benzene. Include the type of material suggested in Question 1.

3. Write a discussion of the halogenation of benzene. Include the type of material suggested in Question 1.

4. Why does dilute nitric acid not serve as an effective nitrating agent?
5. What are the roles of sulfuric acid in nitration of aromatic compounds?
6. What is the role of iron or aluminum in the halogenation of aromatic compounds? Why is a carrier necessary for most hydrocarbons?
7. Write structural formulas or equations which illustrate the following concepts.

- | | |
|--|------------------------------|
| a. <i>meta</i> -directing group | c. protection of amino group |
| b. <i>ortho</i> , <i>para</i> -directing group | |

8. Show how, starting with benzene, one should proceed to synthesize the following compounds. Use structural formulas.

- | | |
|--|---|
| a. <i>p</i> -bromobenzenesulfonyl chloride | d. <i>m</i> -chlorobenzenesulfonic acid |
| b. <i>m</i> -bromobenzenesulfonyl chloride | e. <i>p</i> -bromonitrobenzene |
| c. <i>p</i> -chlorobenzenesulfonic acid | f. <i>m</i> -bromonitrobenzene |
| | g. <i>m</i> -bromoaniline |
| | h. sulfanilic acid |

9. Show how the following compounds can be prepared in good yield from the indicated starting materials. Use structural formulas.

- | | |
|--|--|
| a. 2-aminotoluene-5-sulfonic acid from <i>o</i> -toluidine | c. β -naphthol from naphthalene |
| b. α -naphthol from naphthalene | d. <i>m</i> -chlorobenzotrichloride from toluene |

10. Draw the structural diagram for each of the following compounds. Indicate with arrows pointing to the positions in the diagrams where an electrophilic reagent would be likely to attack. State whether the compound would be more or less reactive than benzene.

- | | |
|-----------------------|-----------------|
| a. aniline | f. acetophenone |
| b. anilinium chloride | g. benzoic acid |
| c. phenol | h. acetanilide |
| d. sodium phenoxide | i. anisole |
| e. benzaldehyde | j. ethylbenzene |

11. Show how the following compounds can be prepared from suitable hydrocarbons. Use structural formulas for organic compounds and indicate reagents and essential conditions.

- | | |
|---|--------------------------------------|
| a. benzyl alcohol | e. 1,3-dinitro-2,5-dimethylbenzene |
| b. 1-chloro-1-phenylethane | f. 2,4-dinitrochlorobenzene |
| c. TNT | g. <i>p</i> -chlorophenol |
| d. <i>p</i> -chloro- <i>o</i> -bromotoluene | h. sodium <i>p</i> -toluenesulfonate |

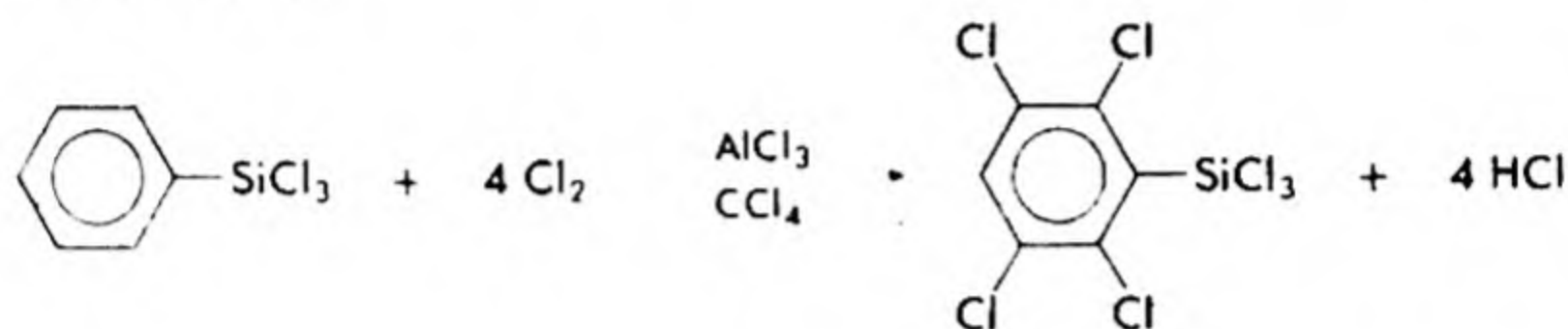
12. Write the structural formula for the main organic product which would be obtained in each of the following reactions.

- | | |
|--|--|
| a. nitration of toluene (1 mole of each reagent) | b. bromination of acetanilide (1 mole of each reagent) |
|--|--|

- c. nitration of acetanilide (1 mole of each reagent).
- d. bromination of toluene with iron catalyst (1 mole each of toluene and bromine)
- e. chlorination of nitrobenzene
- f. sulfonation of acetanilide
- g. treatment of phenol with excess bromine water

13. Explain why one of the reactions in Question 12 proceeds to give the product you have indicated.

14. Suggest an explanation for the orienting effect of the silicon atom as shown by the reaction below. Bear in mind that silicon is less electronegative than carbon and that the silicon atom can utilize $3d$ orbitals in pi bond formation with conjugated double bonds.



15. Write a discussion of side reactions which may be important in the preparation of the following compounds by substitution. Tell what side reactions can occur, giving formulas for typical by-products, and point out how these can be avoided or minimized if possible.

- a. α -naphthalenesulfonic acid
- b. *p*-bromotoluene
- c. *n*-butylbenzene
- d. *p*-bromoacetanilide

16. Write equations for any reactions that occur in the following mixtures of reagents. Indicate essential conditions. Use structural formulas for organic compounds.

- a. anthracene + benzoyl chloride
- b. benzene + bromine
- c. benzene + phosphorus trichloride
- d. benzene + nitric acid
- e. benzene + chlorosulfonic acid
- f. dimethylaniline + sodium nitrite + hydrochloric acid
- g. mesitylene + sulfuric acid
- h. toluene + phosphoric acid
- i. benzene + hydrogen chloride
- j. naphthalene + iodine

17. Write equations for the following reactions. Use structural formulas for the main products and organic reactants.

- a. sulfonation of benzene
- b. sulfonation of *p*-xylene
- c. naphthalene and chlorosulfonic acid.
- d. biphenyl and chlorosulfonic acid (*para* position)
- e. nitric acid and acetic anhydride
- f. nitric acid and concentrated sulfuric acid
- g. nitration of durene
- h. nitration of anthracene (in acetic anhydride; the normal reaction)

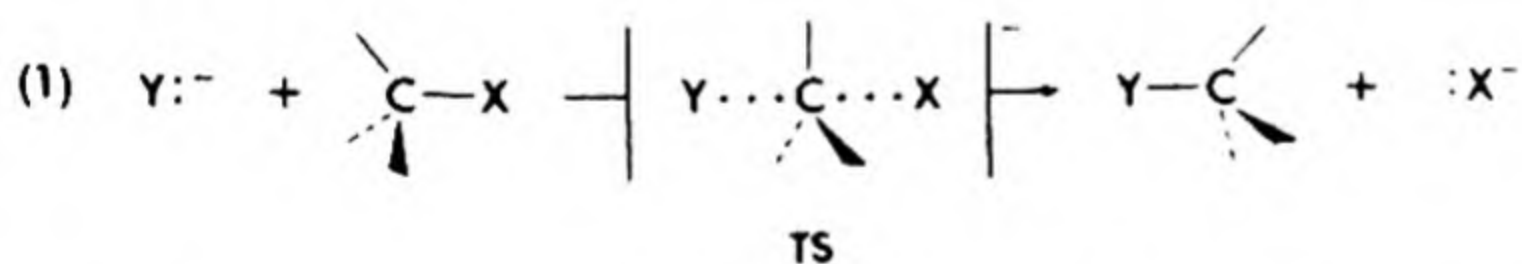
17

Nucleophilic Additions and Displacements at Unsaturated Atoms

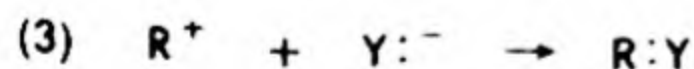
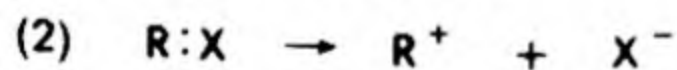
I. Additions and Displacements in Acid Derivatives: Solvolysis

17-1 NUCLEOPHILIC DISPLACEMENT REACTIONS. ADDITION-ELIMINATION MECHANISM

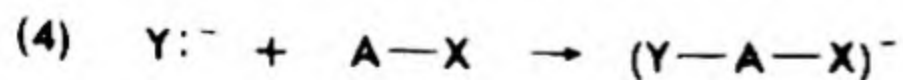
In Chapter 12 it was shown that two principal mechanisms govern nucleophilic displacements at saturated carbon atoms. In direct displacement (eq. 1), the entrance of the nucleophile is concerted with the de-



parture of the leaving group. The carbonium ion process involves the separation of the leaving group first (eq. 2) and then the entrance of the nucleophile (eq. 3).

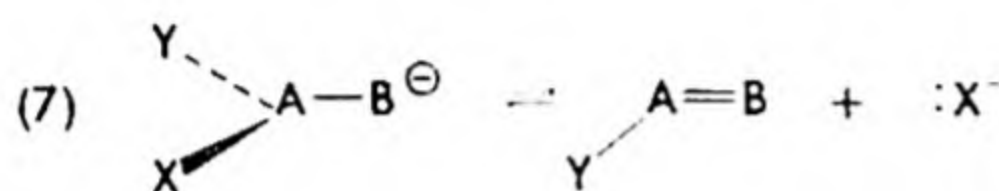
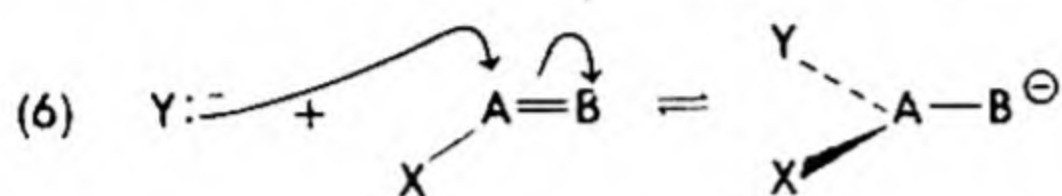


A third mechanistic possibility involves the entrance of the nucleophile before separation of the leaving group (eq. 4), followed later by loss of the displaceable group (eq. 5). Such a process has an intermediate (a low point in a reaction coordinate-energy diagram) formed in the first step, which in some cases can be isolated or readily detected. Such inter-

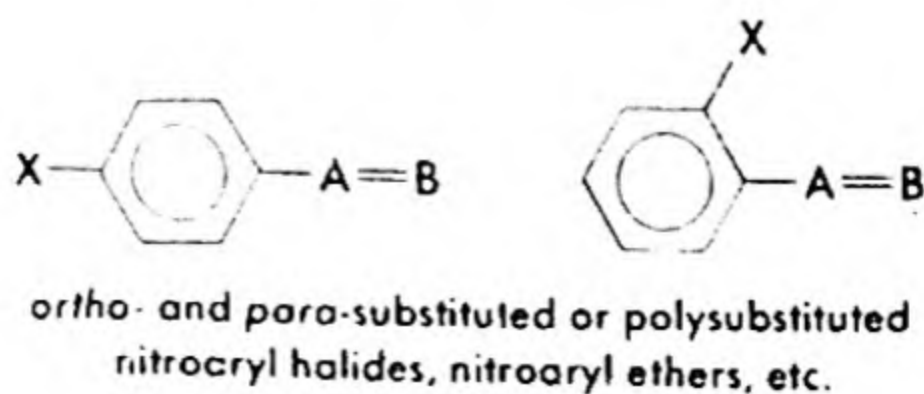
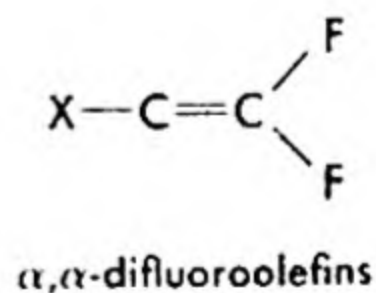
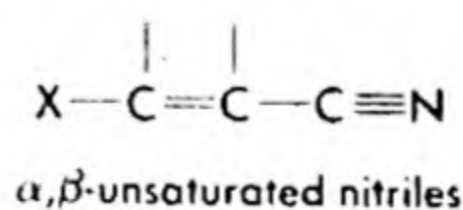
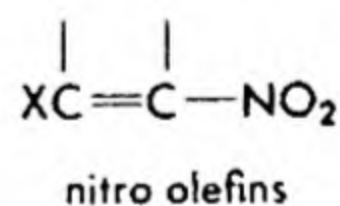
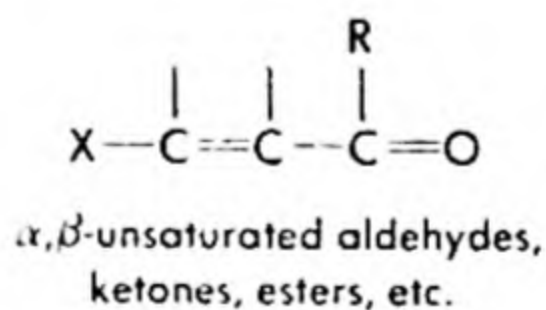
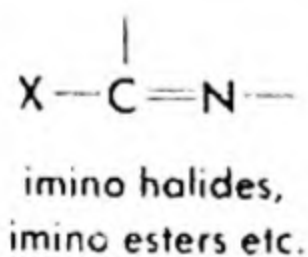
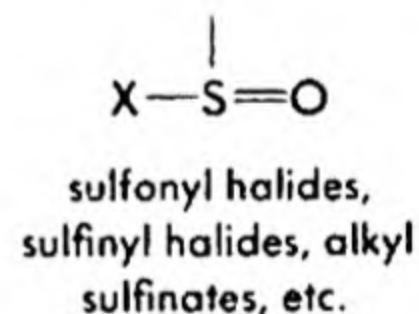
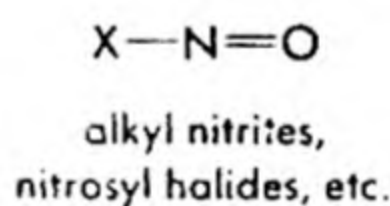
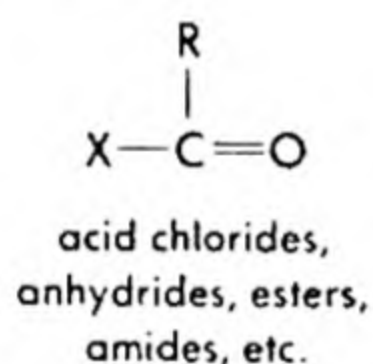


mediates cannot be involved in displacements on saturated (tetrahedral) carbon atoms, where there are insufficient stable atomic orbitals available to accommodate the five groups that would be present around the carbon atom, but are usually involved in displacements on unsaturated atoms (such as trigonal or linear carbon atoms) or atoms in higher rows of the periodic table (e.g., silicon, phosphorus) where orbitals are available to permit bonding to more atoms than are bonded in the initial substrate.

Most such reactions may be further generalized as in eqs. (6) and (7).



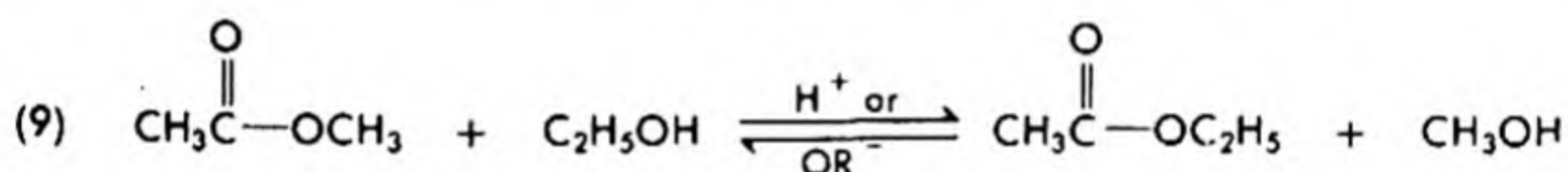
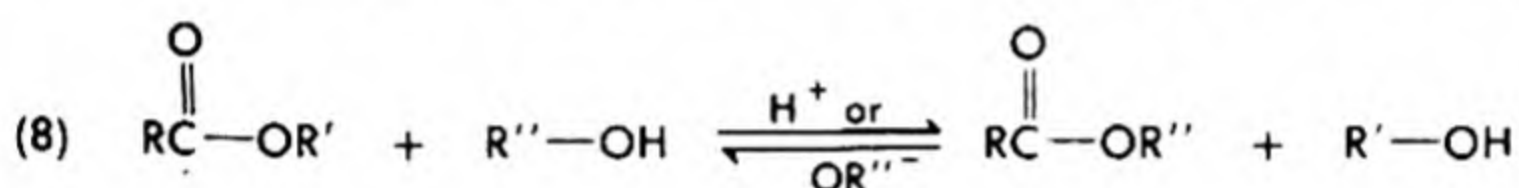
In principle, Y may be any nucleophile, and A and B any of a variety of atoms or groups. In the intermediate (and therefore in the transition state leading to it), electrons accumulate on atom B of the electrophilic A=B system. Thus, reactions of this type go well when the A=B bond is readily polarizable in such a fashion that the B atom willingly accepts the extra electron pair (or has a means to delocalize it), and goes poorly or not at all when such is not the case. Examples of favorable XAB systems are as follows:



As protonation of the B atom (or coordination with a Lewis acid) leads to stabilization of the electron pair on B, reactions of this sort are often subject to acid catalysis. Basic catalysis is also often observed, as for example, when the solvent is $\text{HY}:$ and base produces $:\text{Y}:^-$, which is a better nucleophile than $\text{HY}:$.

17-2 ESTER INTERCHANGE AS A TYPICAL NUCLEOPHILIC DISPLACEMENT

When an ester, such as methyl acetate, is treated with an alcohol, such as ethanol, the alkyl groups interchange, in this case to form ethyl acetate (eq. 9). The reaction, called *ester interchange* or *transesterification*, is reversible, with the position of equilibrium dependent upon the relative concentrations of the two alcohols. These reactions do not proceed at useful rates in the absence of catalysts, even at reflux temperatures, but go when small amounts of strong acid (e.g., hydrochloric, sulfuric,



p-toluenesulfonic acids) or of strong base (potassium or sodium alkoxide) are added. There is convincing evidence that the base-catalyzed reactions proceed by the path shown in eqs. (10), (11), and (12) (Fig. 17-1), while

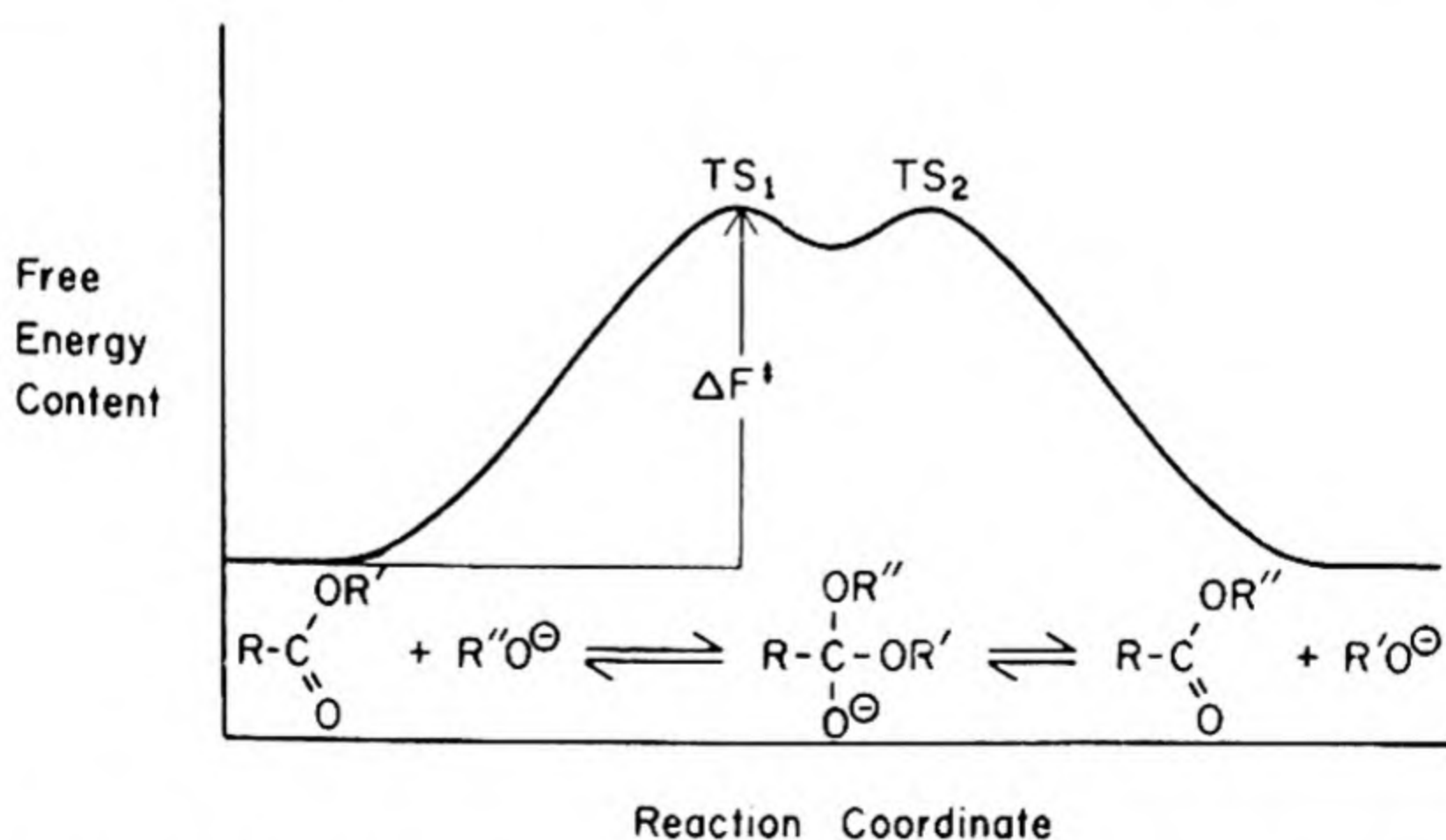


Fig. 17-1. Energy Diagram for Base-Promoted Transesterification. Slight changes in relative levels of the reagents, intermediate, and products generalize this energy system for any such process.

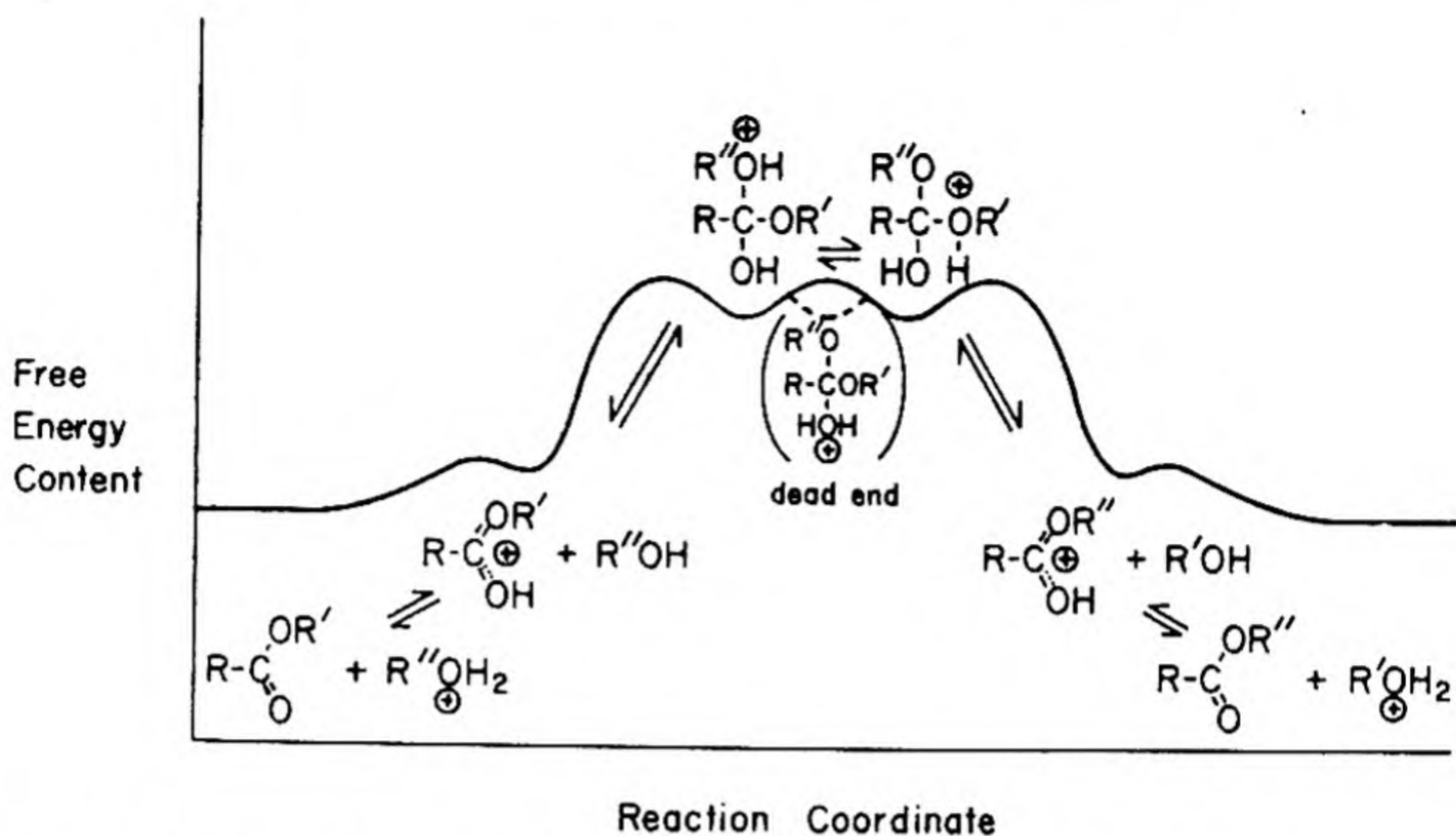
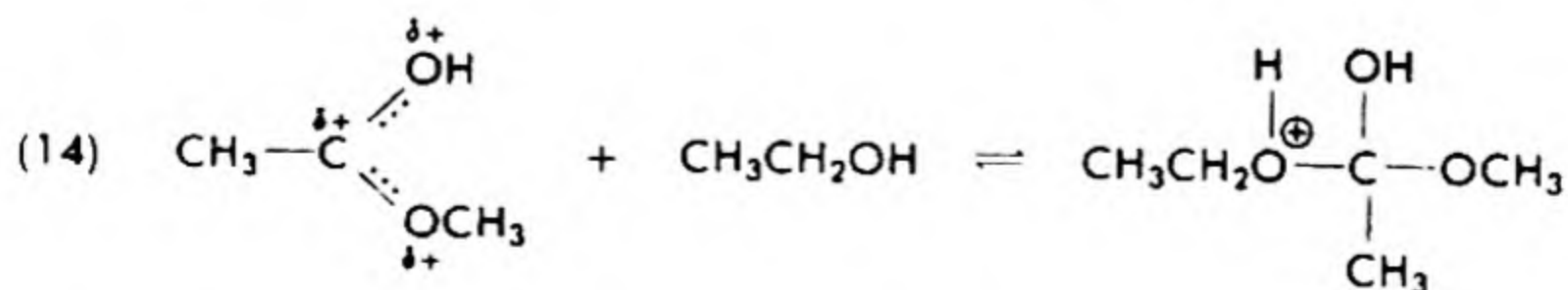
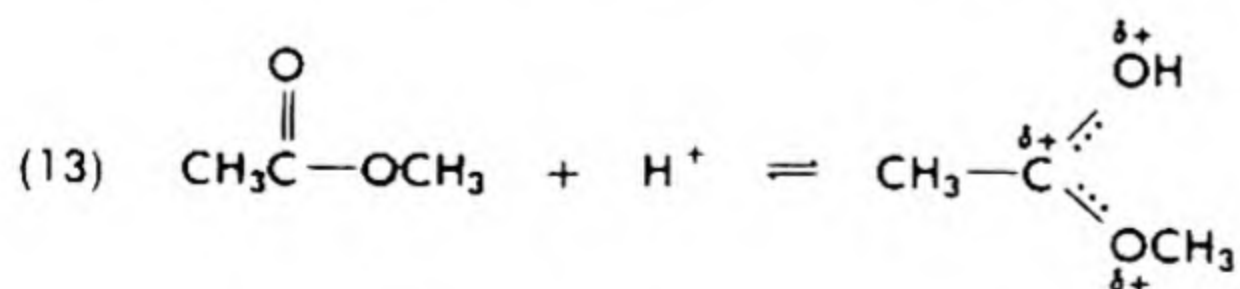
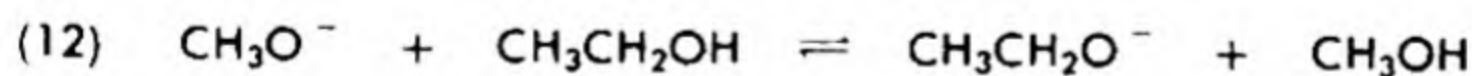
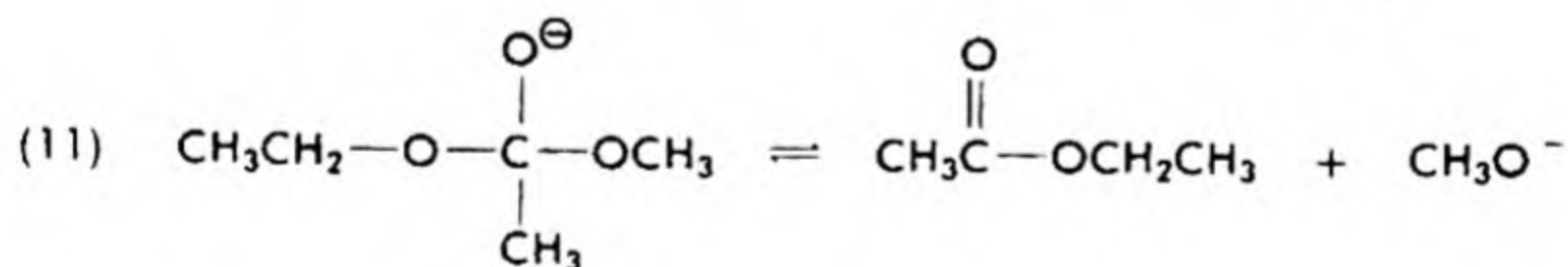
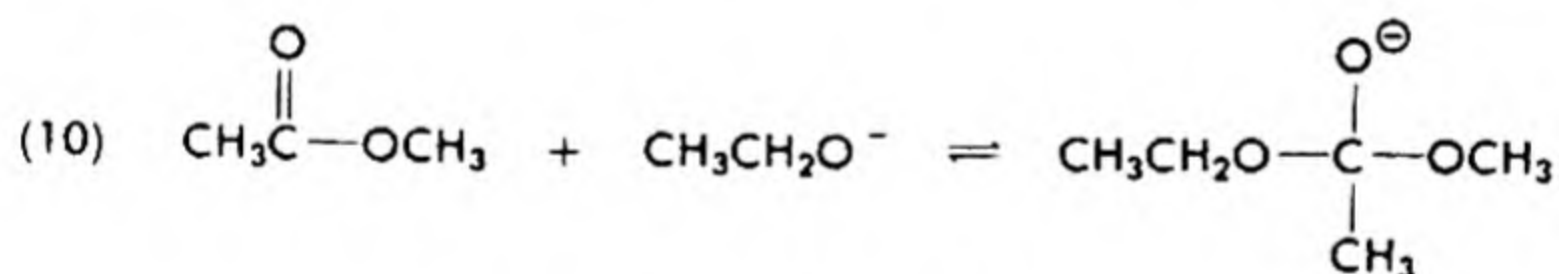
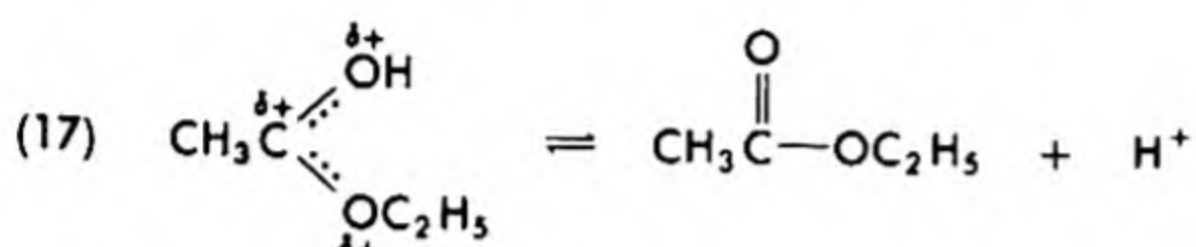
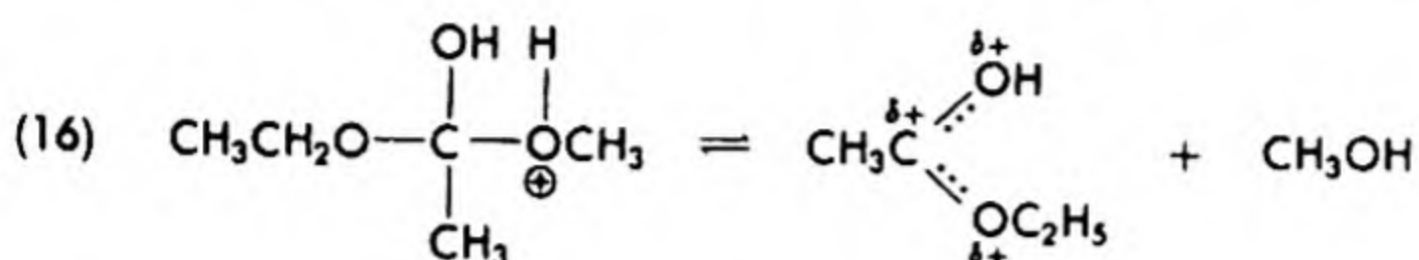
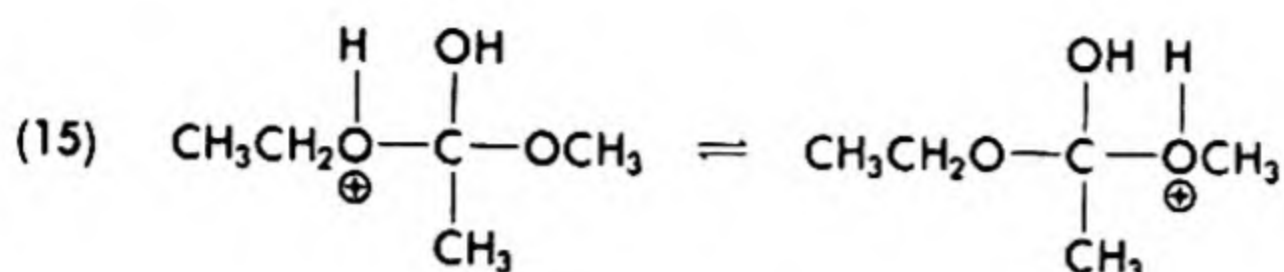


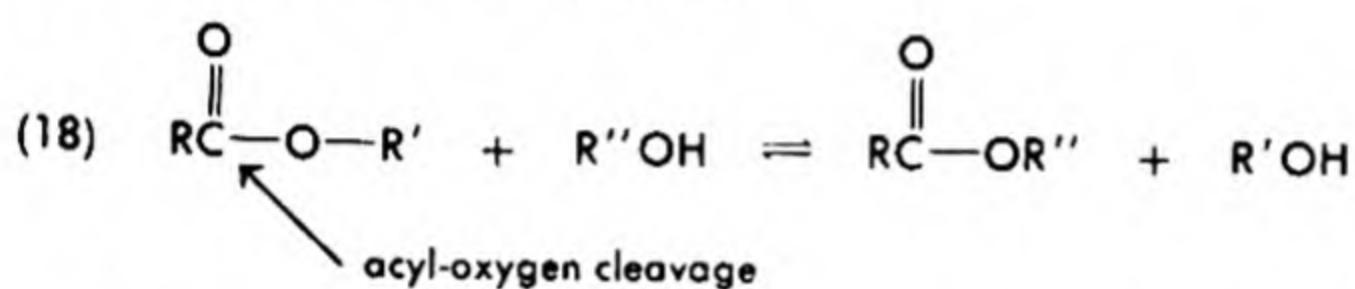
Fig. 17-2. Energy Diagram for Acid-Catalyzed Transesterification. Slight changes in relative levels of reagents, the various intermediates, and products generalize this energy system for any such process.

that involving acid catalysis proceeds as shown in eqs. (13) to (17) (Fig. 17-2).

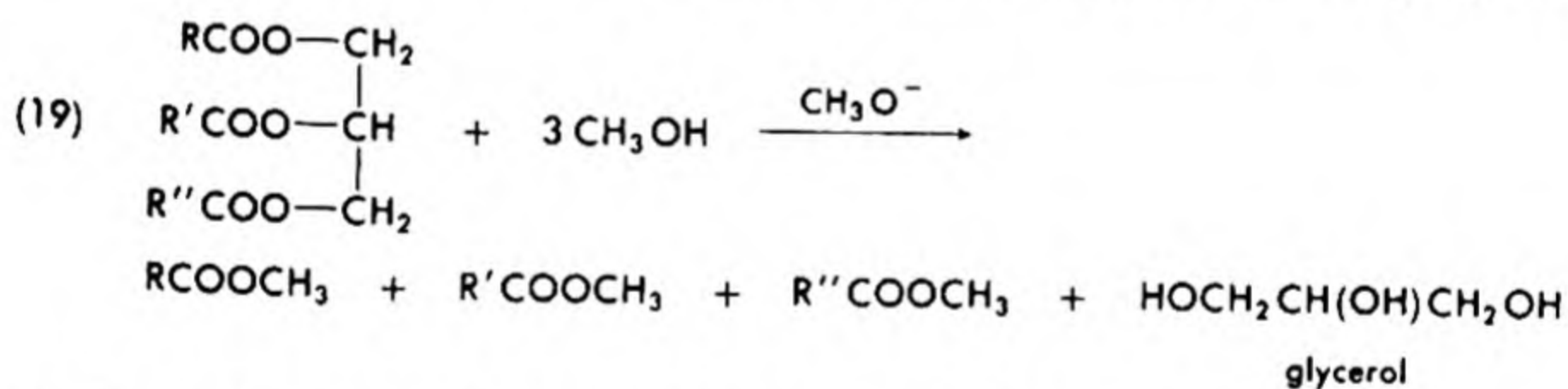




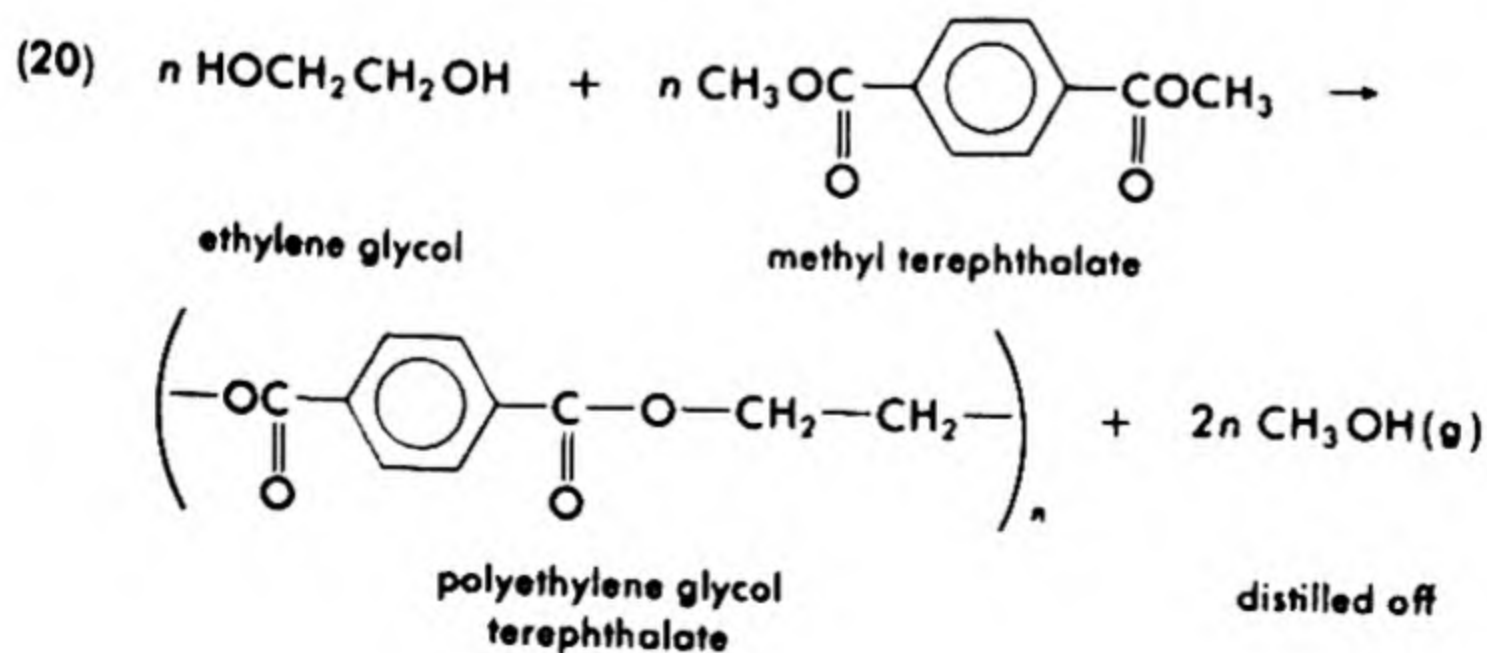
Note that in both the acid- and base-catalyzed reactions, displacement has occurred between the acyl group and the alkoxy group, that is, with acyl-oxygen cleavage (eq. 18).



Transesterification is used industrially in the formation of fatty acid esters and glycerol from fats (eq. 19) and in the formation of the polyester,



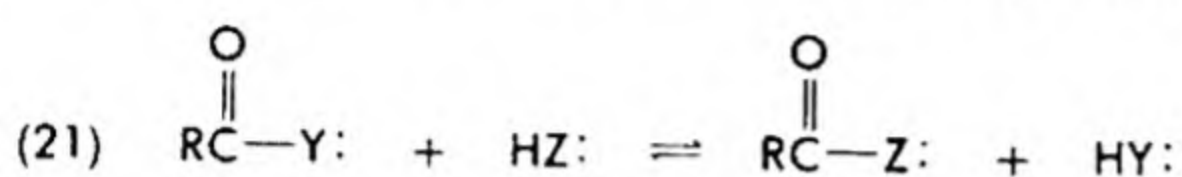
used as a fiber or a film (Dacron and Mylar), from ethylene glycol and dimethyl terephthalate (eq. 20).



17-3 SOLVOLYSIS OF ACID DERIVATIVES AND ACIDS

Transesterifications are typical of a wide variety of solvolysis reactions involving carboxylic acids and their functional derivatives. Since the reagent and product alcohols and the reagent and product esters in the above examples are, in general, of the same orders of reactivities, there is little internal driving force to bring these equilibria to completion in either direction. However, with different types of nucleophiles and different types of acid derivatives involved, this may not necessarily follow.

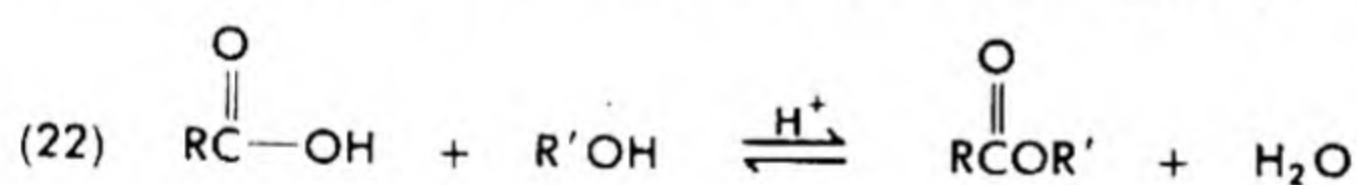
In the equilibrium shown in eq. (21), the position of equilibrium has a



complicated dependence upon the nature of both Y and Z. The reaction will proceed, in the absence of mass law effects, to give the more stable products. In general, the equilibrium is shifted in the desired direction by adjustment of reagent concentrations or by removal of products (distillation, precipitation, further chemical reaction).

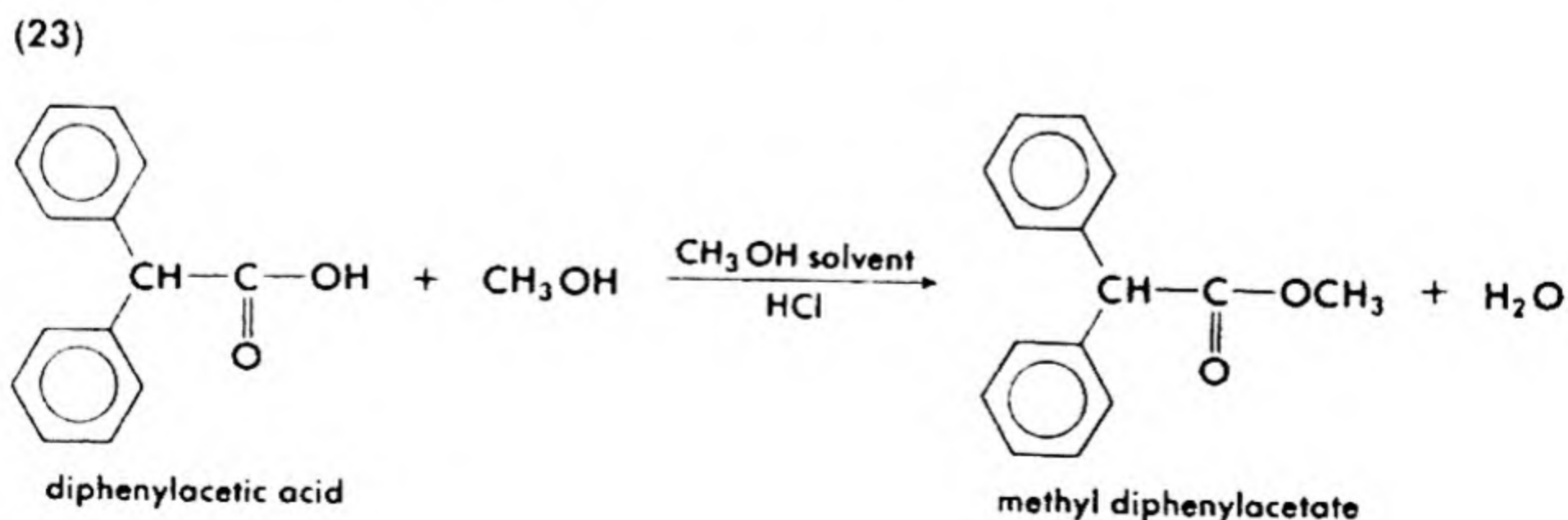
A. Acid-Catalyzed Formation and Hydrolysis of Esters

When mixtures of alcohols and carboxylic acids are heated in the presence of strong acids, esters are formed (eq. 22). When esters and water are treated similarly, the esters are hydrolyzed (reverse of eq. 22).



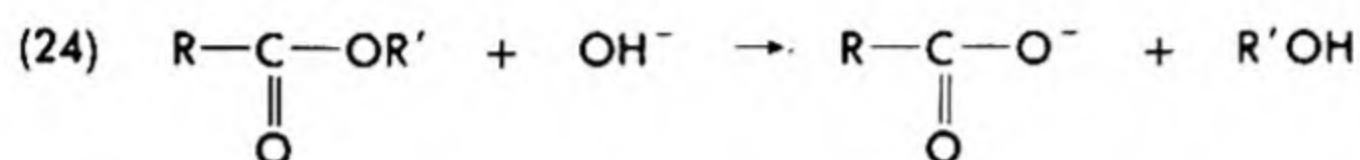
The equilibrium represented in eq. (22) can be displaced to the right by using a large excess of one of the reagents, carboxylic acid or alcohol, and/or by removing one or both of the products.

When the ester of a common, inexpensive alcohol is desired, esterification can be made nearly complete by the use of a large excess of the alcohol as solvent. This procedure is effective for the preparation of methyl diphenylacetate (eq. 23) in quantitative yield.



In many cases, esterification can be driven to completion, even where the equilibrium is unfavorable, by continuous removal of water. Azeotropic distillation with benzene or toluene and the use of a water separator (Fig. 17-3) drives the esterification to completion. Even phenols can be esterified by this method.

Hydrolysis of an ester can be driven to completion either by providing a large excess of water or by removing the acid as it forms with a base. When a strong base is used, the hydroxide ion is the reagent, not molecular water (eq. 24).



The steps in esterification (eqs. 25-29) are precisely analogous to those of ester interchange. The forward reactions relate to esterification and the reverse to hydrolysis. There is, again, first a protonation, then attack by

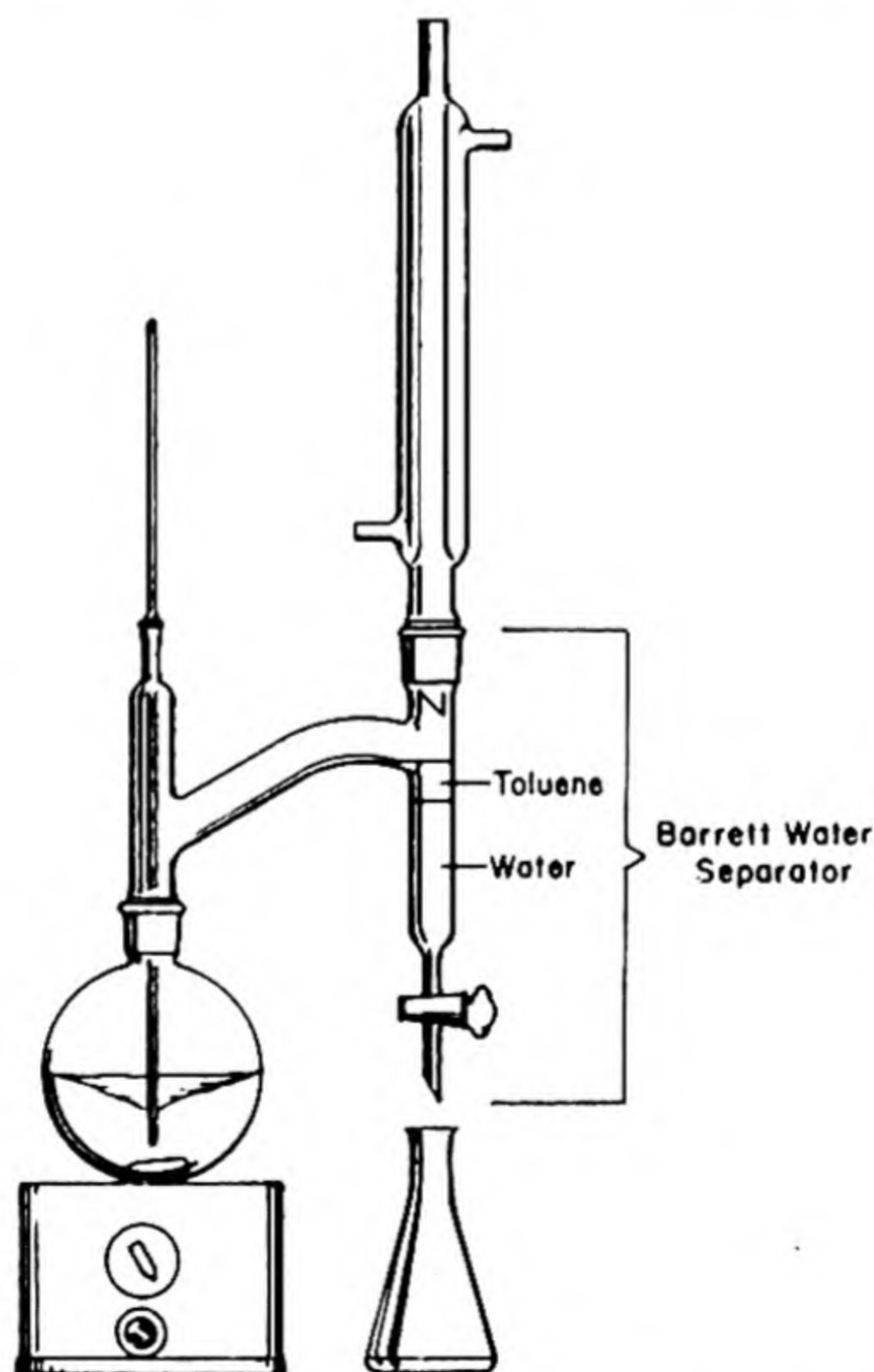
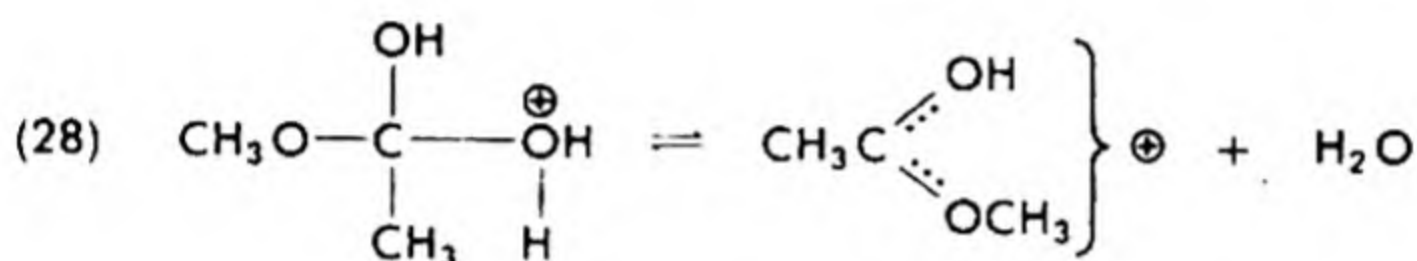
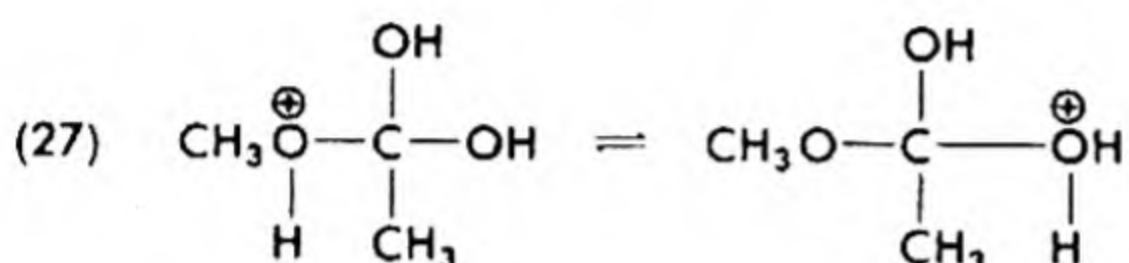
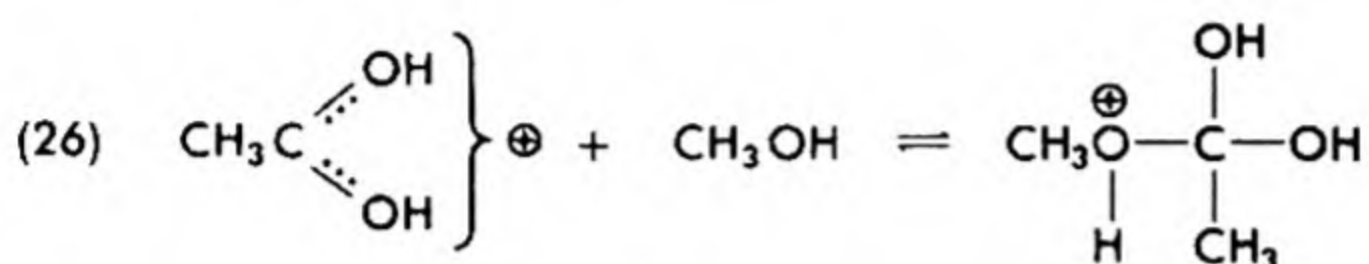
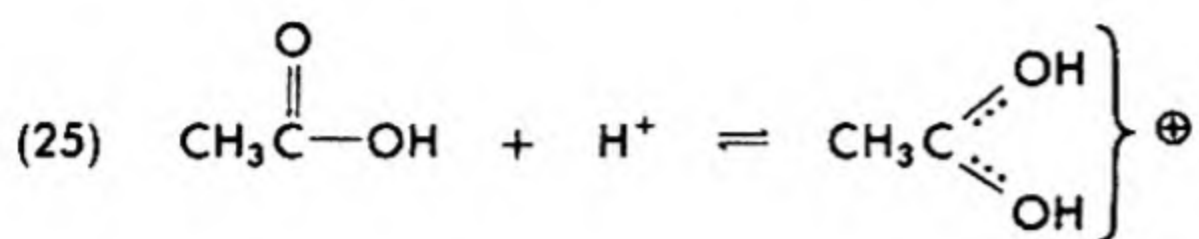


Fig. 17-3. Apparatus with Stripper for Continuous Water Removal.



nucleophile, proton transfer, loss of leaving group, and finally deprotonation with regeneration of the acid catalyst. This mechanism is consistent with each of the following facts:

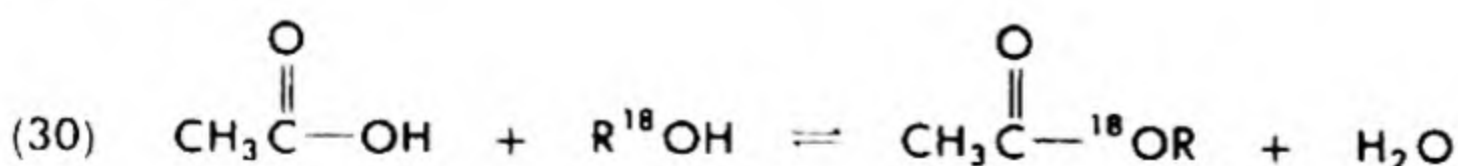
(a) Esterification is first order in carboxylic acid, first order in alcohol, and first order in strong acid.

(b) Hydrolysis is first order in ester, first order in water, and first order in acid.

(c) When an optically active alcohol is used, the ester is formed with retention of configuration; similarly, when the active ester is hydrolyzed, the alcohol retains its configuration.

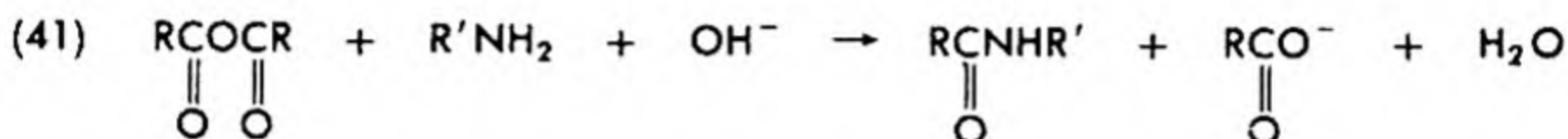
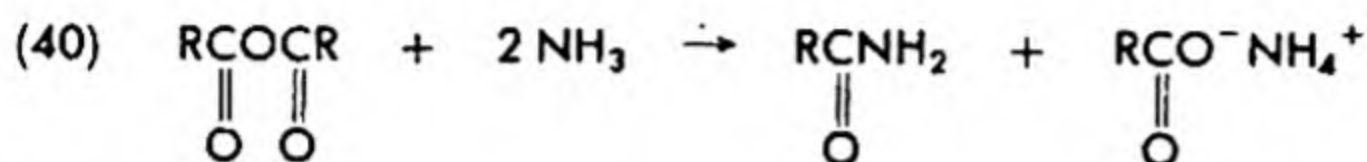
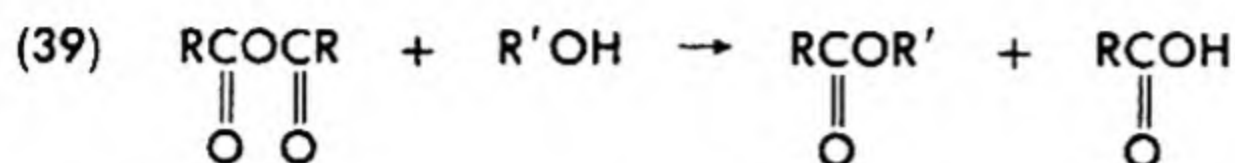
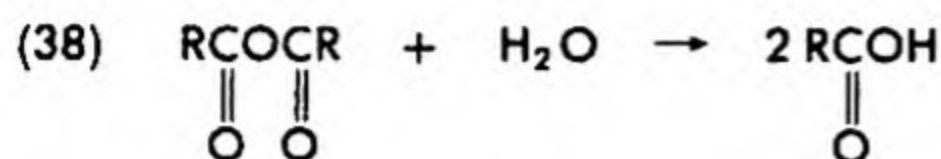
(d) When an alcohol labeled with heavy oxygen is used, the labeled oxygen ends in the ester and not in the water; when this ester is hydrolyzed, it goes into the alcohol and not the acid.

Facts (c) and (d) show clearly that acyl-oxygen cleavage occurs (eq. 30) and that the alkyl-oxygen bond is not affected in normal esterification and hydrolysis.

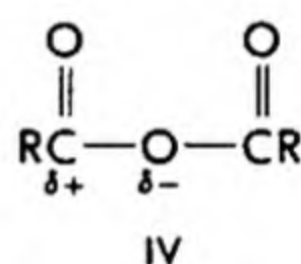
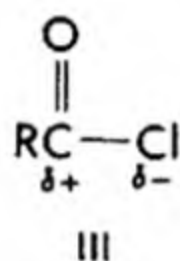


B. Alkaline Hydrolysis of Esters. Saponification

A very common method of hydrolysis of esters involves basic reagents such as sodium or potassium hydroxide and results in the formation of



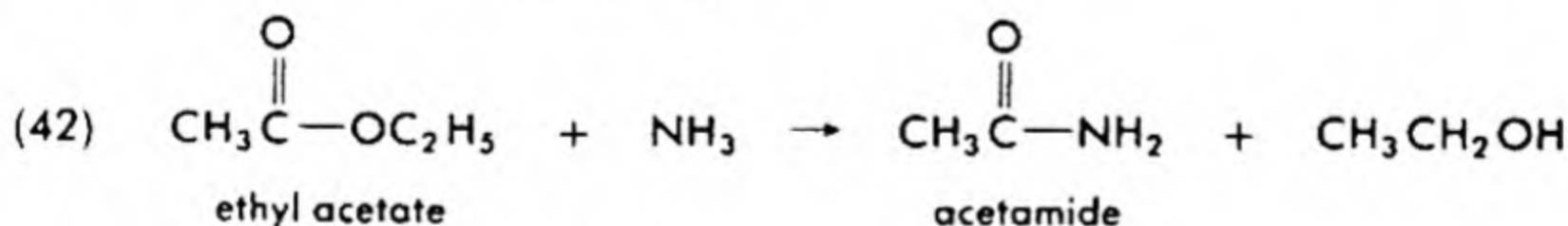
These acid derivatives are more reactive than carboxylic acids or esters because of the greater attraction of the nucleophile to the electrophilic carbon atom when the electron-attracting group or atom is attached (III, IV).



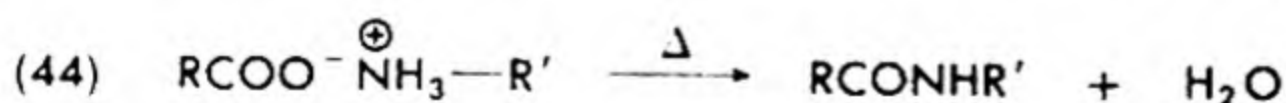
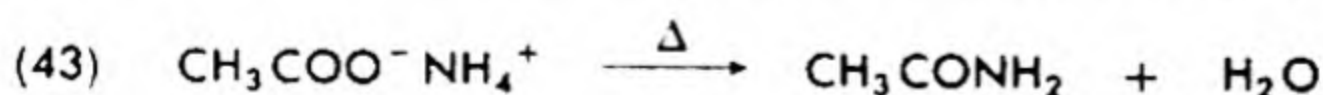
The products are so stable by comparison with the reagents that these reactions are, in practice, irreversible.

D. Amide Formation and Hydrolysis

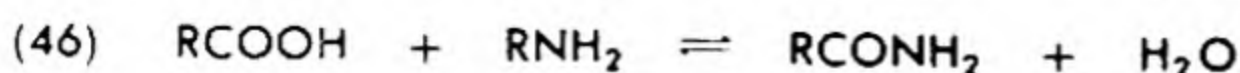
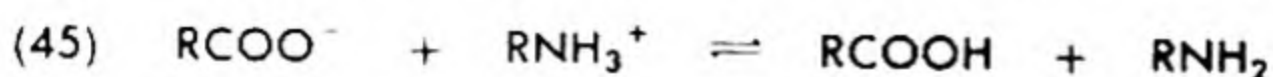
The formation of amides from ammonia or from primary and secondary amines and acid halides, anhydrides, or esters proceeds via the general mechanism for nucleophilic displacements, as do their hydrolyses. As ammonia is a better nucleophile than water, a solution of an ester in aqueous ammonia standing at room temperature for a few days will form the corresponding amide (eq. 42).



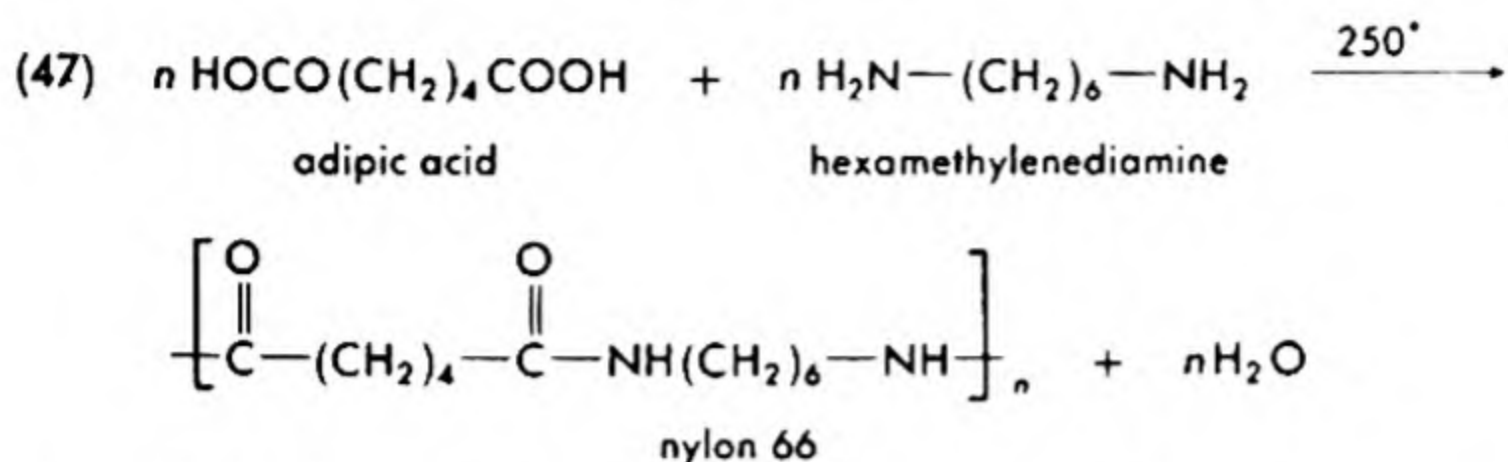
Heating of salts of amines and carboxylic acids at temperatures of 100-250° also results in amide formation (eq. 43). This latter process



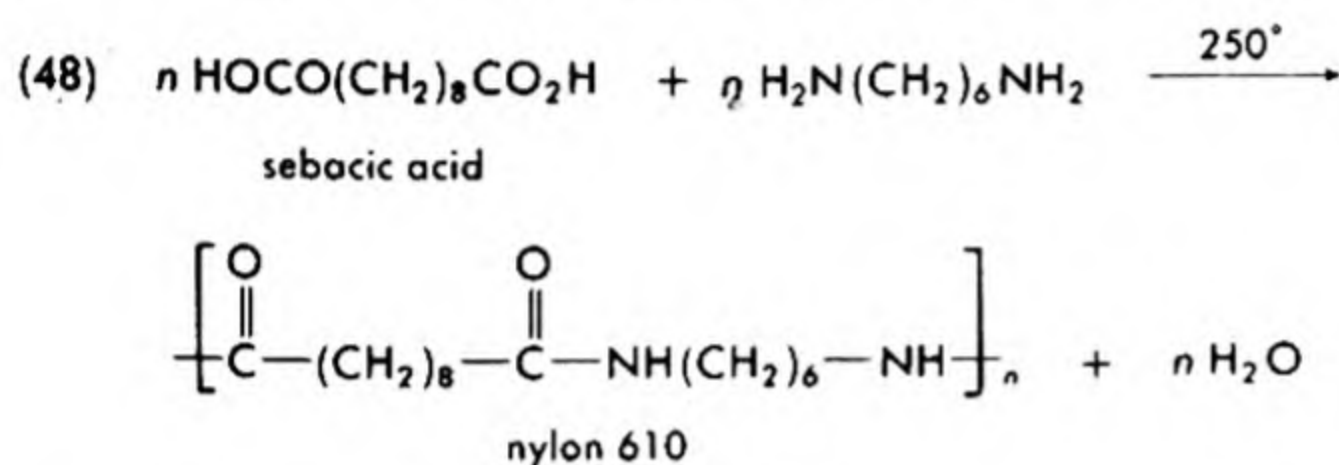
undoubtedly involves the transformations indicated in eqs. (45) and (46),



where the reaction indicated in eq. (46) may be catalyzed by certain Lewis acids. The formation of nylon 66 from hexamethylenediamine and adipic

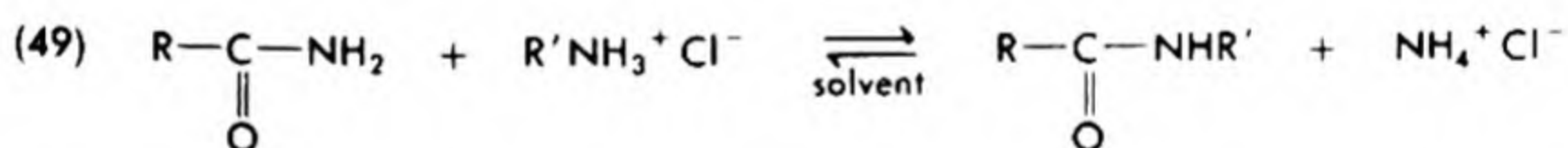


acid (eq. 47) or of nylon 610 from hexamethylenediamine and sebacic acid (eq. 48) represent important industrial applications of these reactions

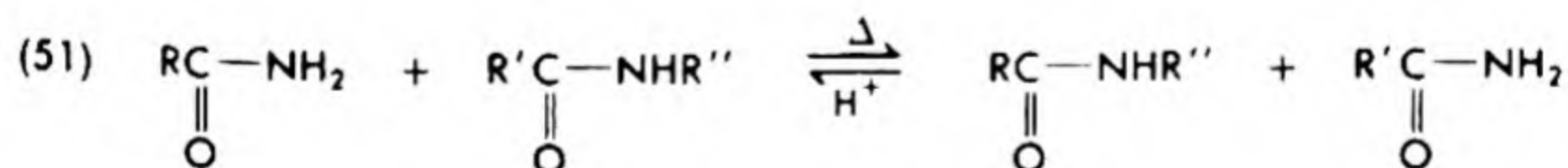
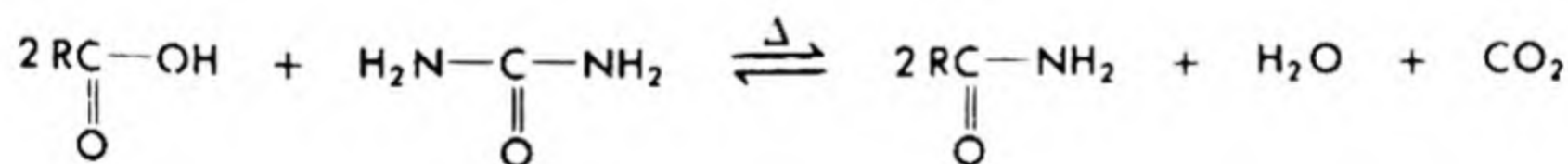


(§46-5B). The molecular weights of these polyamides can be controlled by the amount of water distilled out.

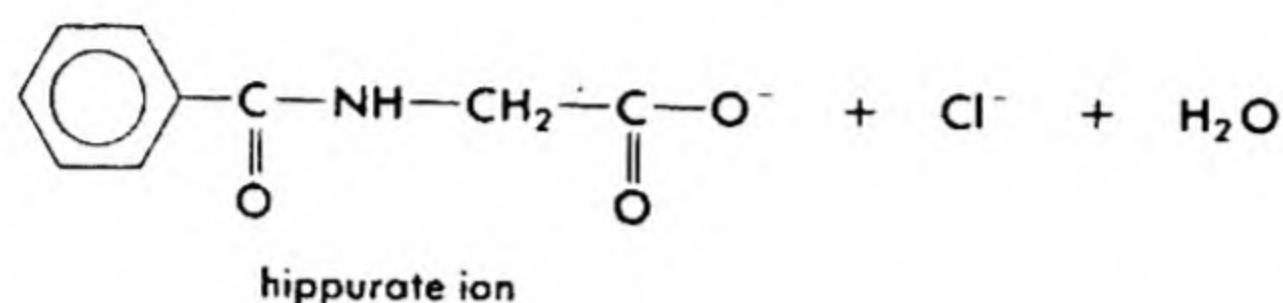
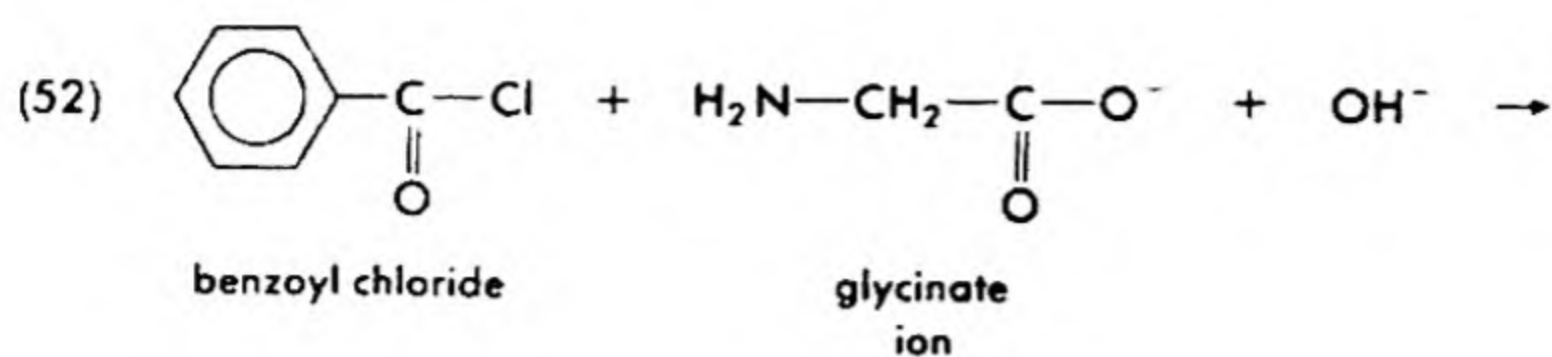
Amide-exchange reactions are sometimes used in synthesis. Here again, either the amine radical or the acyl radical or both can be exchanged (eqs. 49, 50, and 51). These reactions are standard synthetic procedures.



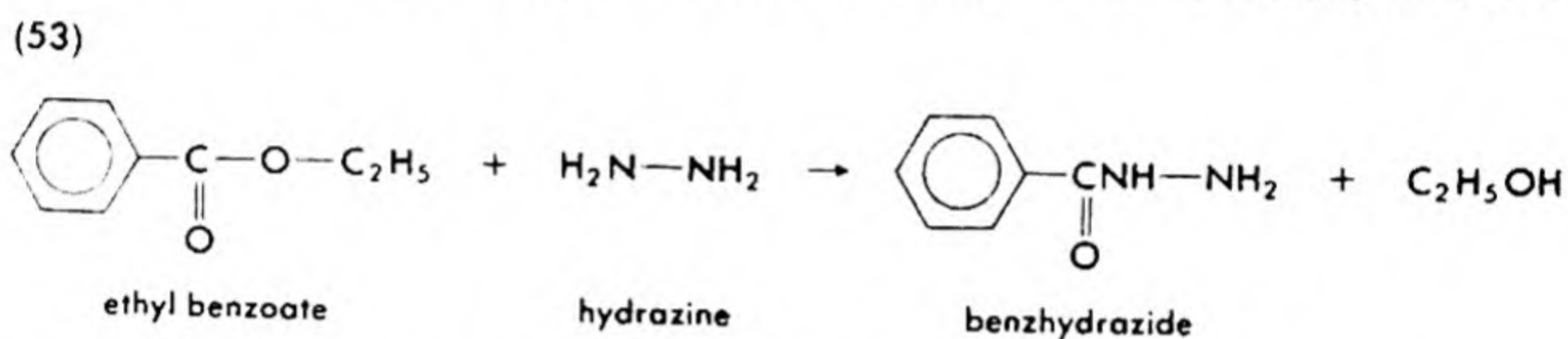
(50)



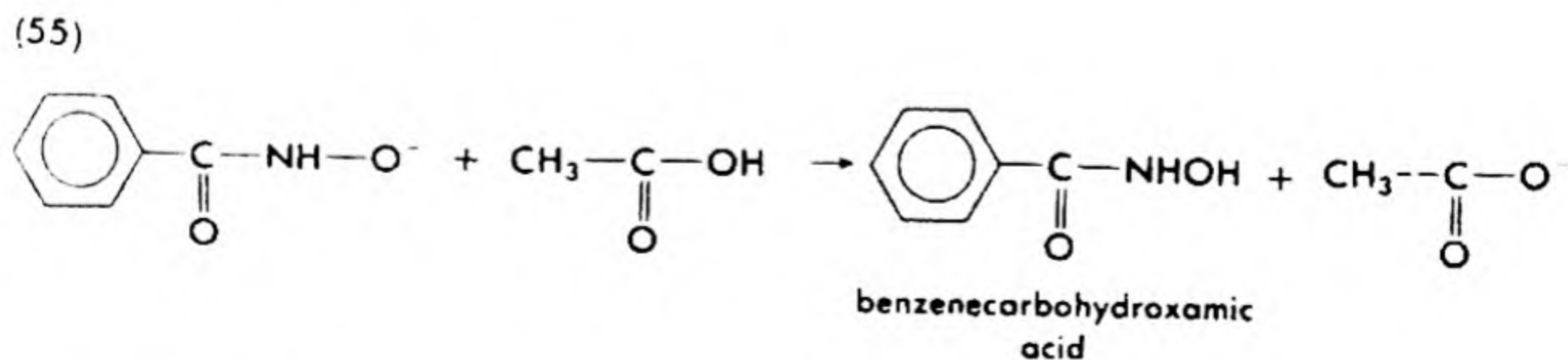
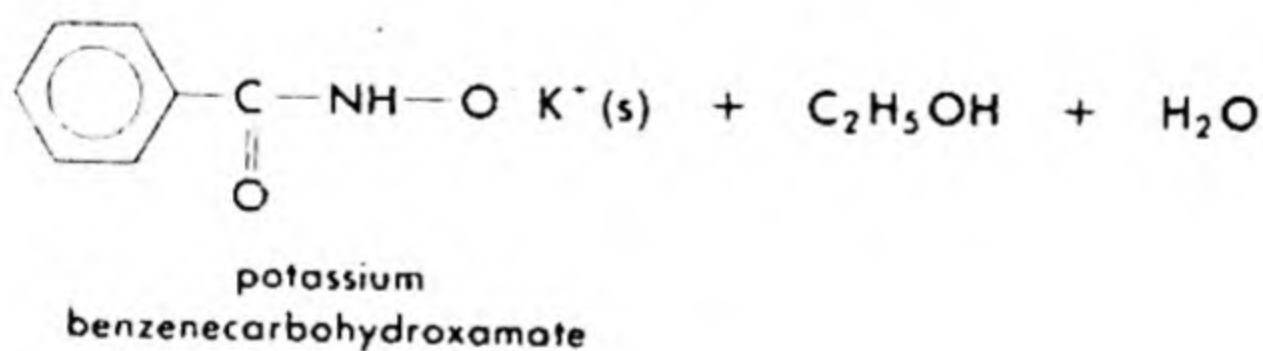
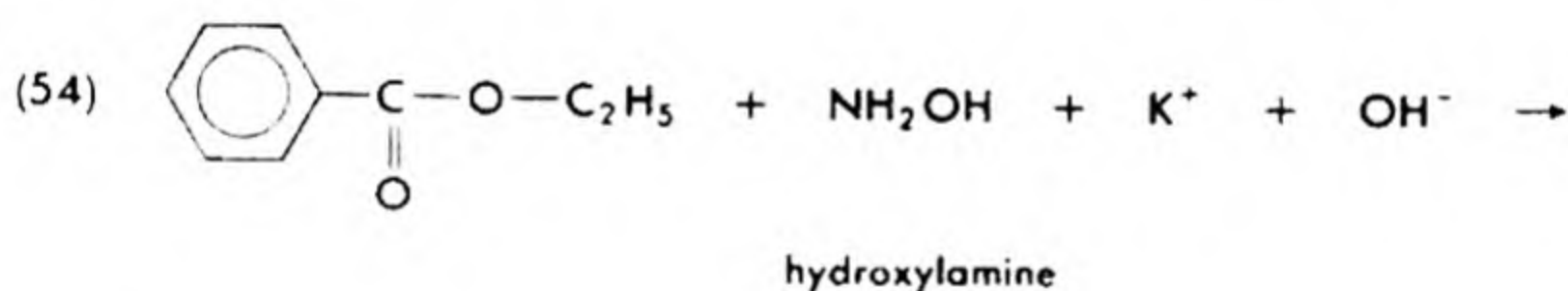
Amide formation from acylhalides and anhydrides is of value in identification of an acid or its halide, as well as a route to many synthetic intermediates of value. To avoid the necessity of using 2 moles of amine, sodium hydroxide or pyridine can be used to neutralize the hydrogen chloride evolved (eq. 52). The use of sodium hydroxide is the *Schotten-Baumann procedure*. Hippuric acid is prepared in 68% yield by this method.



Like amides, hydrazides and hydroxamic acids are readily prepared from esters. Benzhydrazide is obtained in 80% yield from ethyl benzoate. Potassium benzenecarbohydroxamate is obtained in 56–60% yield, and

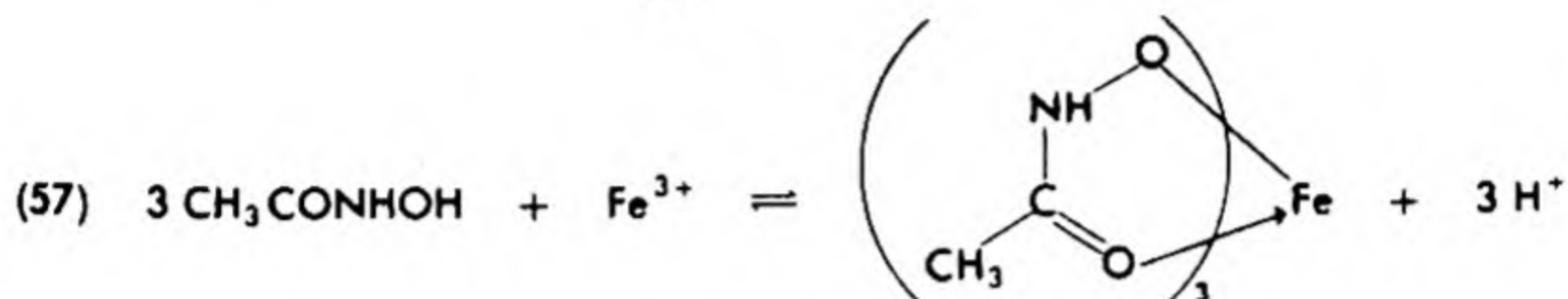
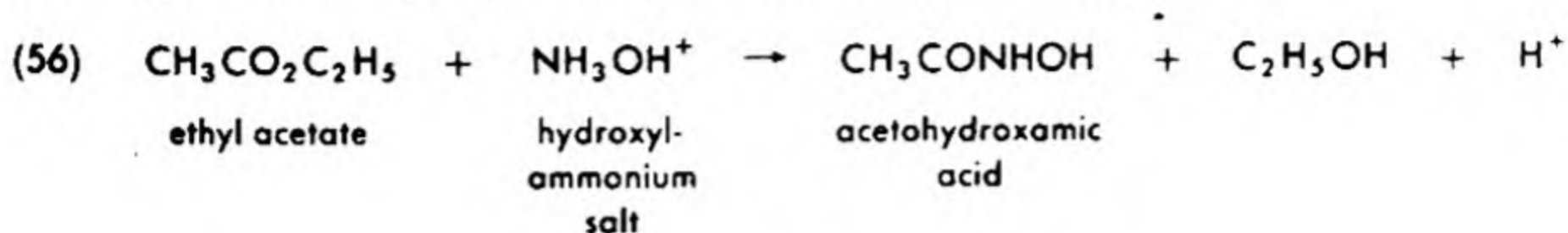


benzenecarbohydroxamic acid in 43–46% overall yield from ethyl benzoate.



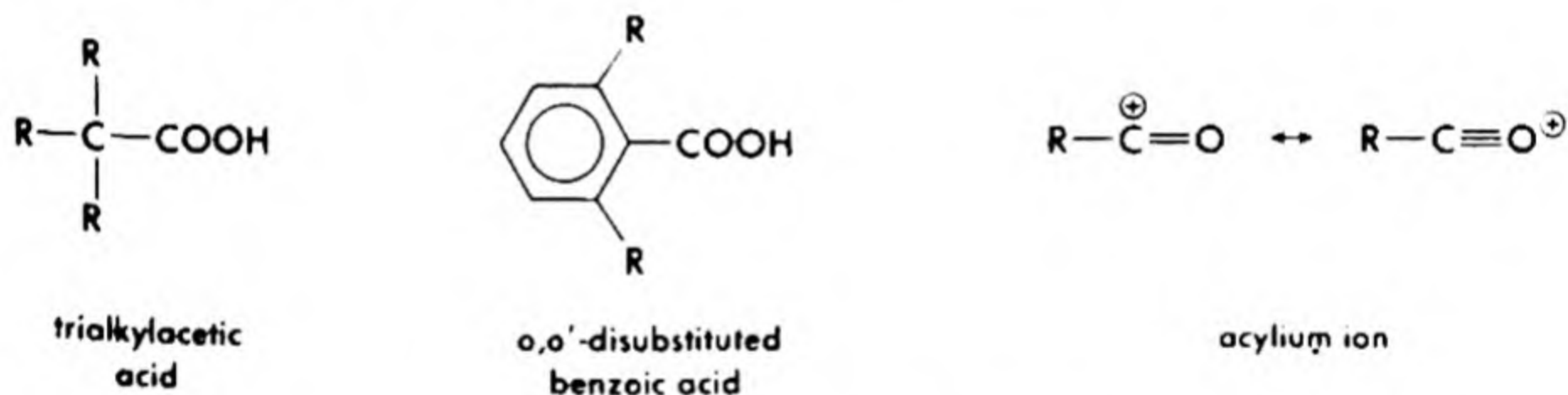
The formation of a hydroxamic acid from an ester, anhydride, or acyl chloride can be used as a qualitative test for these acid derivatives. In

this case, base is not used, and the product is treated with ferric chloride, which gives red or purple complexes with hydroxamic acids.

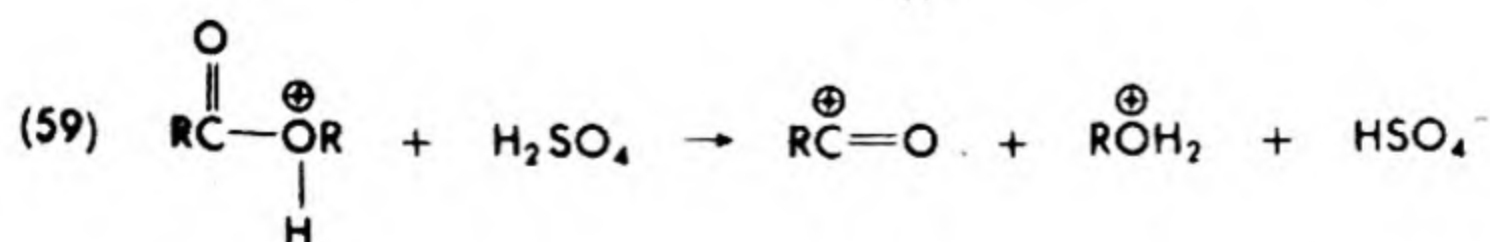
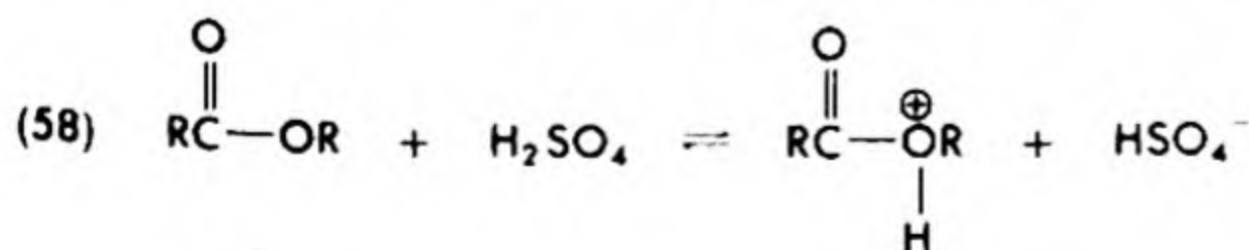


E. Abnormal Solvolysis Mechanisms

In normal solvolysis, the reaction involves the formation of a tetrahedral carbon atom from a trigonal atom. This means that there is more crowding in the transition state than in the reactants; hence, such reactions are subject to steric hindrance. Indeed, derivatives of trialkylacetic acids and *o,o'*-disubstituted benzoic acids are quite unreactive. Even the acyl halides react very sluggishly.



Solvolyses involving these acyl groups therefore utilize another mechanism for which these compounds are especially reactive. The compound is dissolved in 100% sulfuric acid, which converts the acid or ester to an acylium ion (eqs. 58 and 59). This solution is then poured rapidly onto ice (for hydrolysis) or into an alcohol (for esterification) (eqs. 60 and 61). The formation of the acylium ion is promoted in "hindered" acids and their derivatives because steric strains are reduced by formation of the linear acylium ions. (See the energy diagram, Fig. 17-4.)



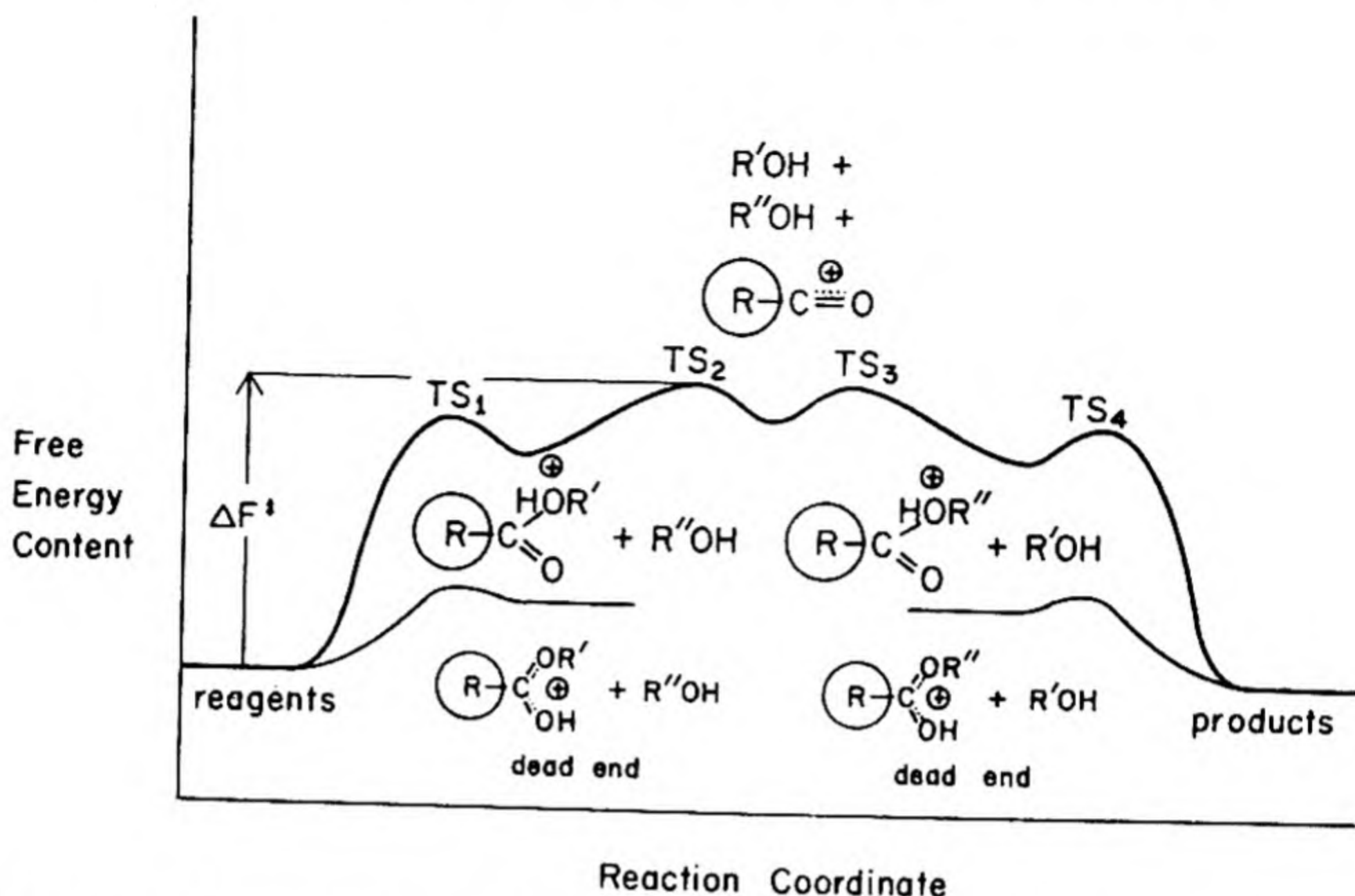
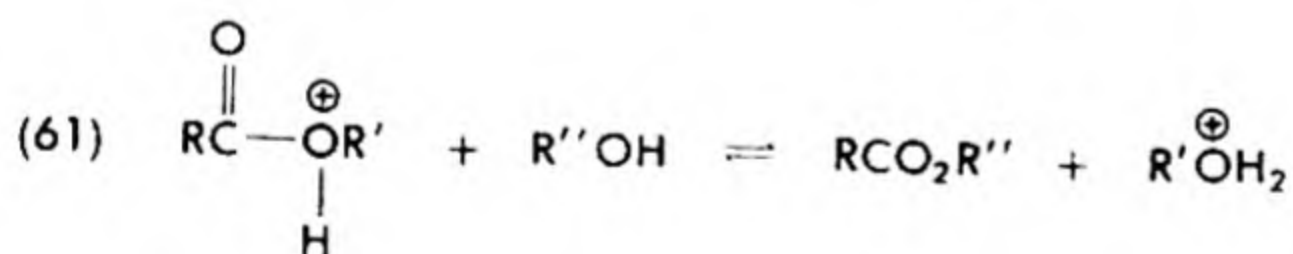
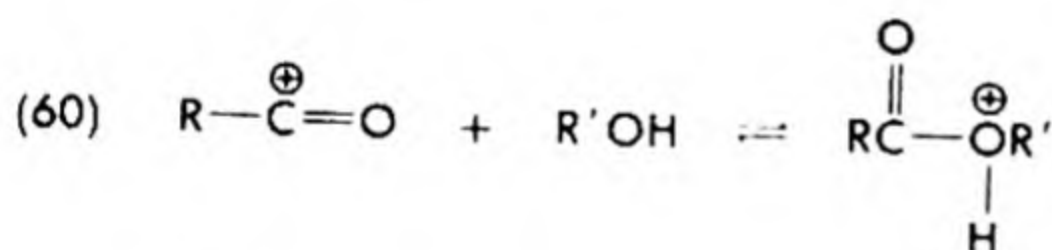
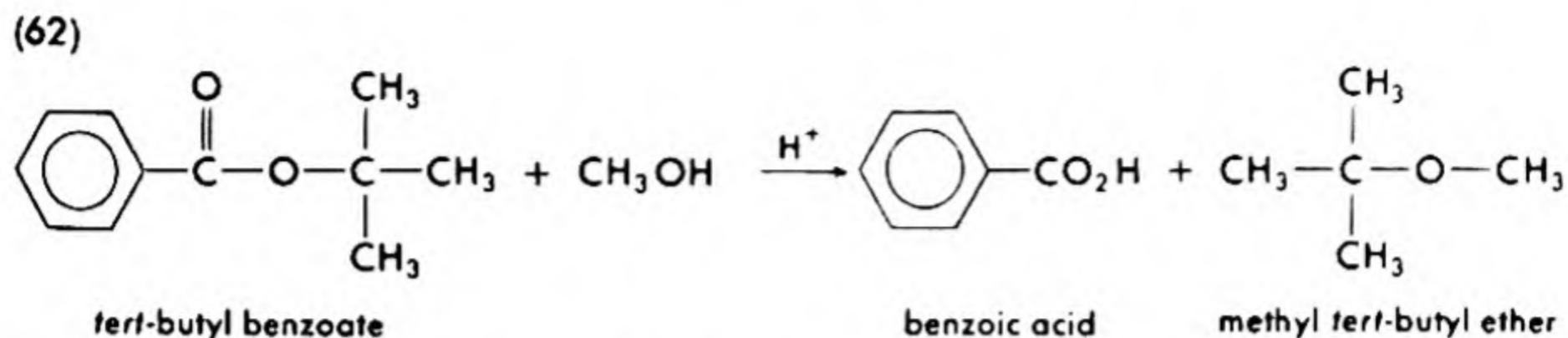


Fig. 17-4. Energy Diagram for Abnormal Transesterification. Slight changes in relative levels of reagents, intermediates, and products generalize this energy system for any such process.

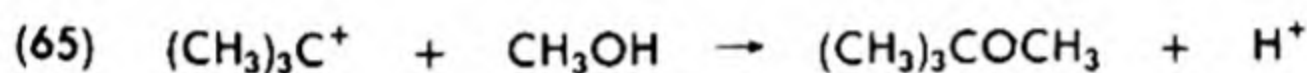
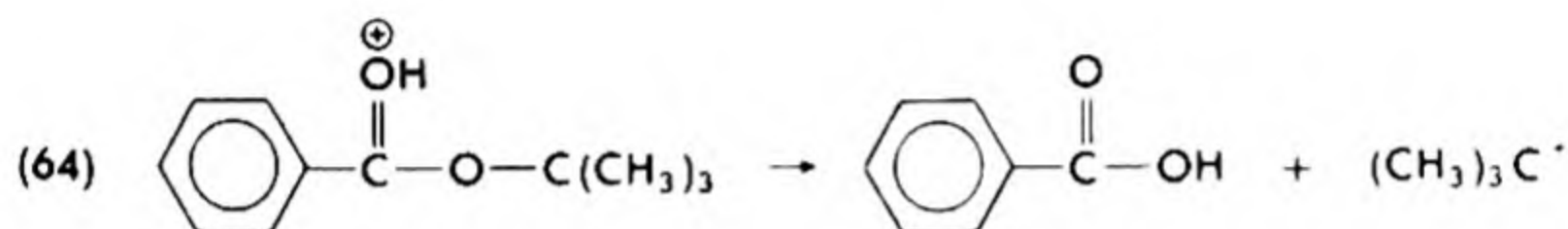
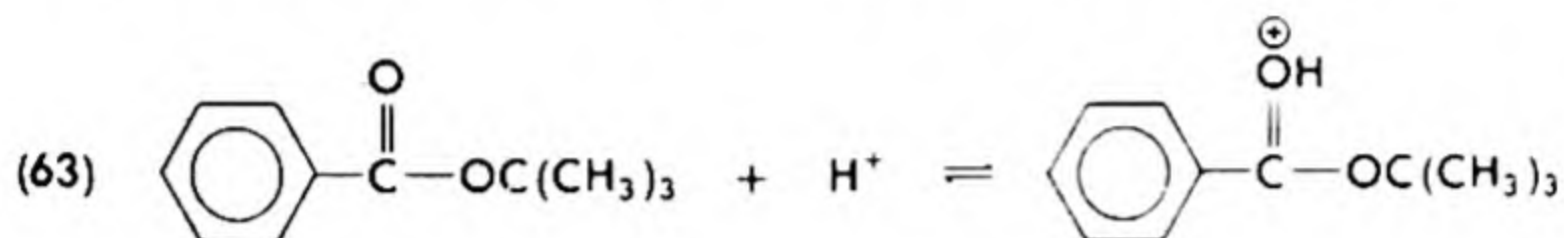


Steric effects are also observed with respect to the nucleophile. Thus, simple primary alcohols are esterified more rapidly than secondary. Tertiary alcohols are usually difficult to esterify via these procedures, as they are highly hindered from esterification, but are very sensitive to acid-catalyzed carbonium ion reactions.

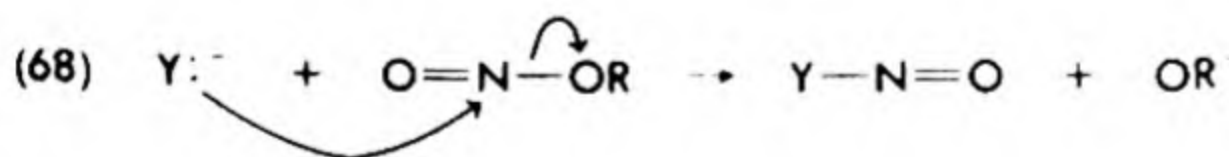
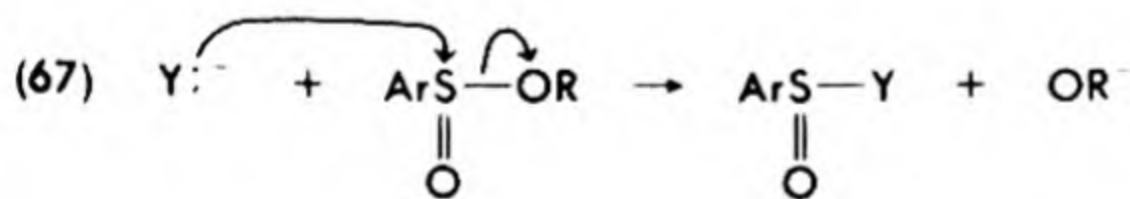
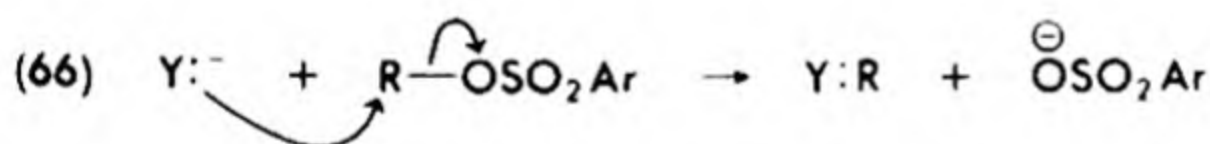
The mechanisms discussed thus far involve acyl-oxygen cleavage. When alkyl groups are present that give very stable carbonium ions, alkyl-oxygen cleavage may be observed. Thus *tert*-butyl benzoate, on treatment with methanol and mineral acid, gives *tert*-butyl methyl ether and benzoic acid, rather than *tert*-butyl alcohol and methyl benzoate, the products of normal solvolysis (eq. 62).



This involves the reaction path shown in eqs. (63) to (65).



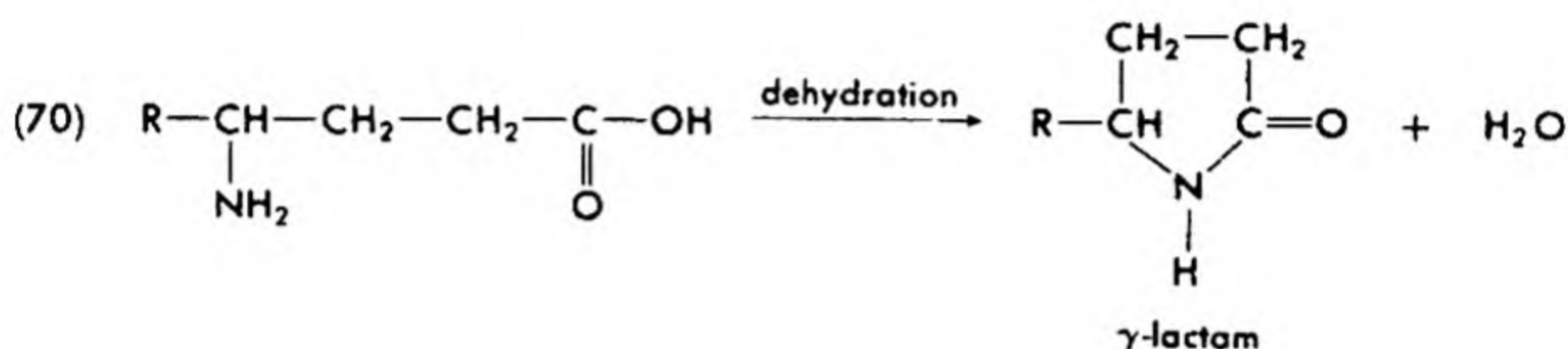
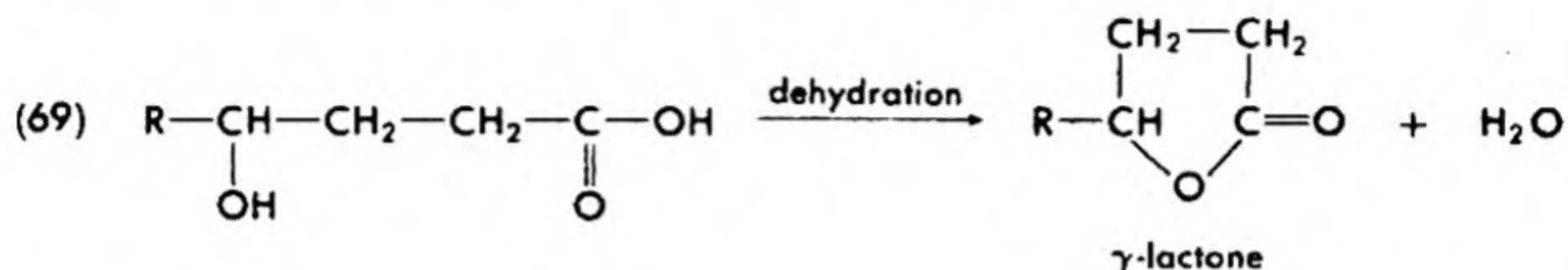
The hydrolysis of sulfonate esters, as described in Chapter 12, as well as other nucleophilic displacement reactions of these compounds, also involve alkyl-oxygen cleavage and are therefore examples of nucleophilic displacements on saturated carbon atoms rather than on unsaturated sulfur atoms (eq. 66). Sulfinates (eq. 67) react with retention of configuration and are like carboxylic esters; nitrite esters react similarly (eq. 68).



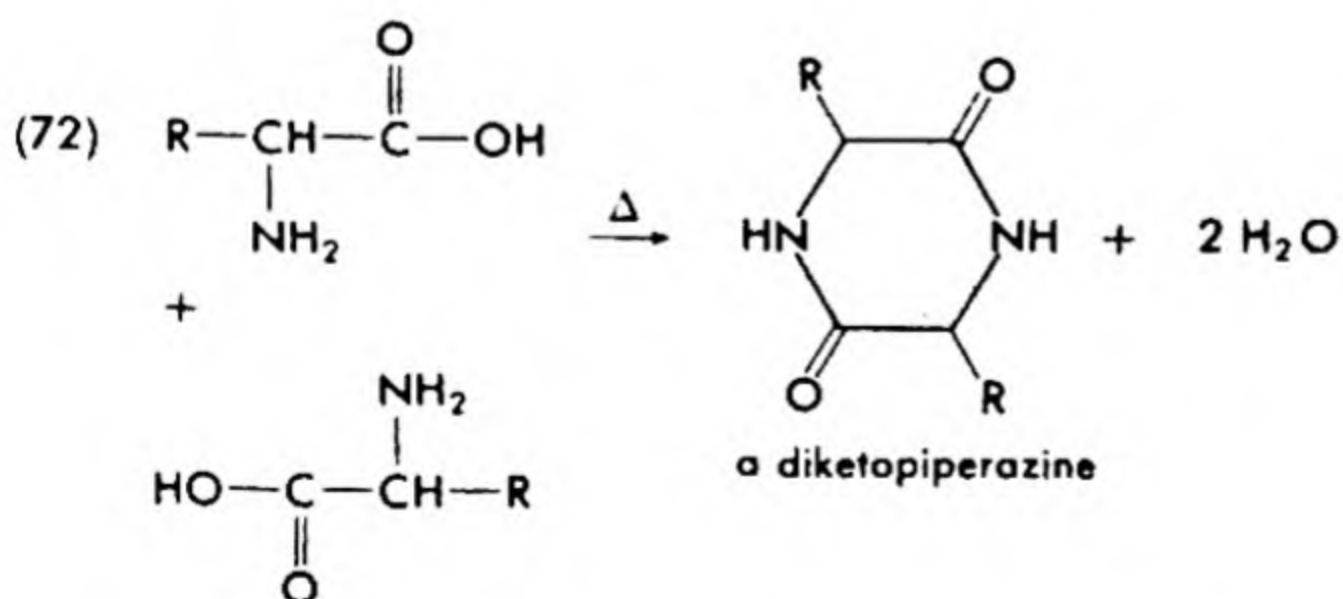
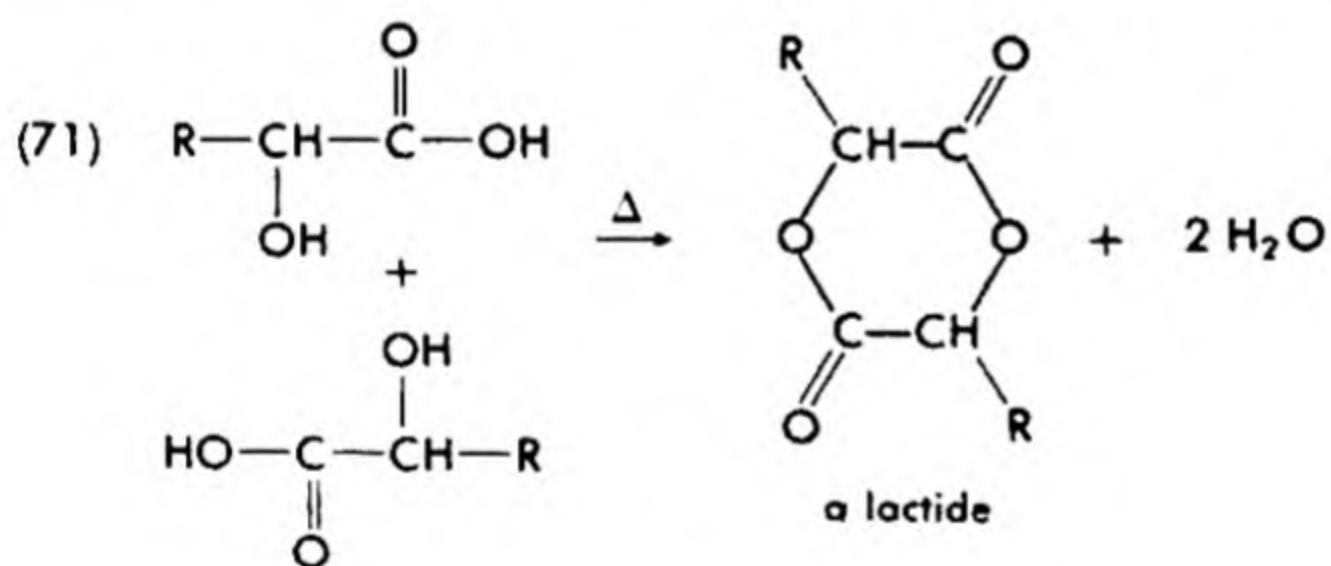
F. Cyclization Reactions. Lactones and Lactams

Whenever cyclization forms five- or six-membered rings, the products are unusually stable and easily formed. Cyclization within a molecule requires the nucleophilic group to have the γ or δ position to the carbonyl group. Thus, γ - and δ -hydroxy acids and γ - and δ -amino acids cyclize very readily. The inner esters are called lactones, the inner amides,

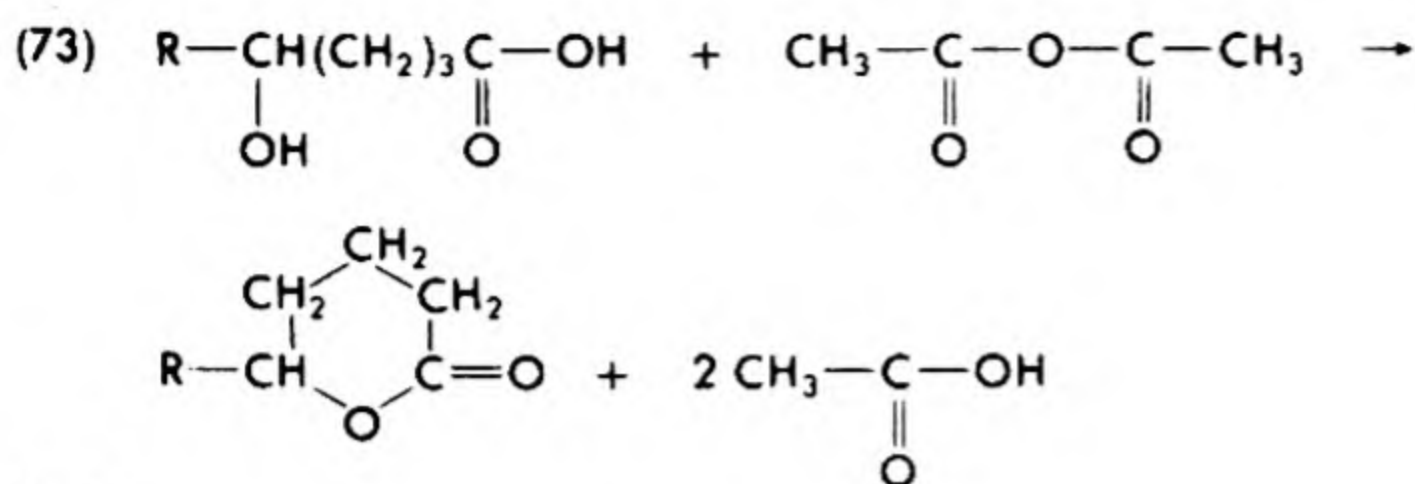
lactams. Formation of lactones or lactams is brought about by gentle heating, presence of even mild dehydrating agents such as acetic anhydride, or mild acid catalysis (eqs. 69 and 70).



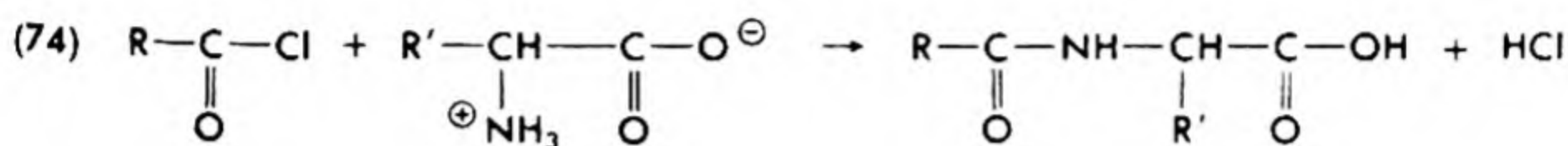
Cyclization between two molecules readily occurs when the solvolytic group occupies the α -position. α -Hydroxy acids form lactides (eq. 71) and α -amino acids form diketopiperazines (eq. 72).



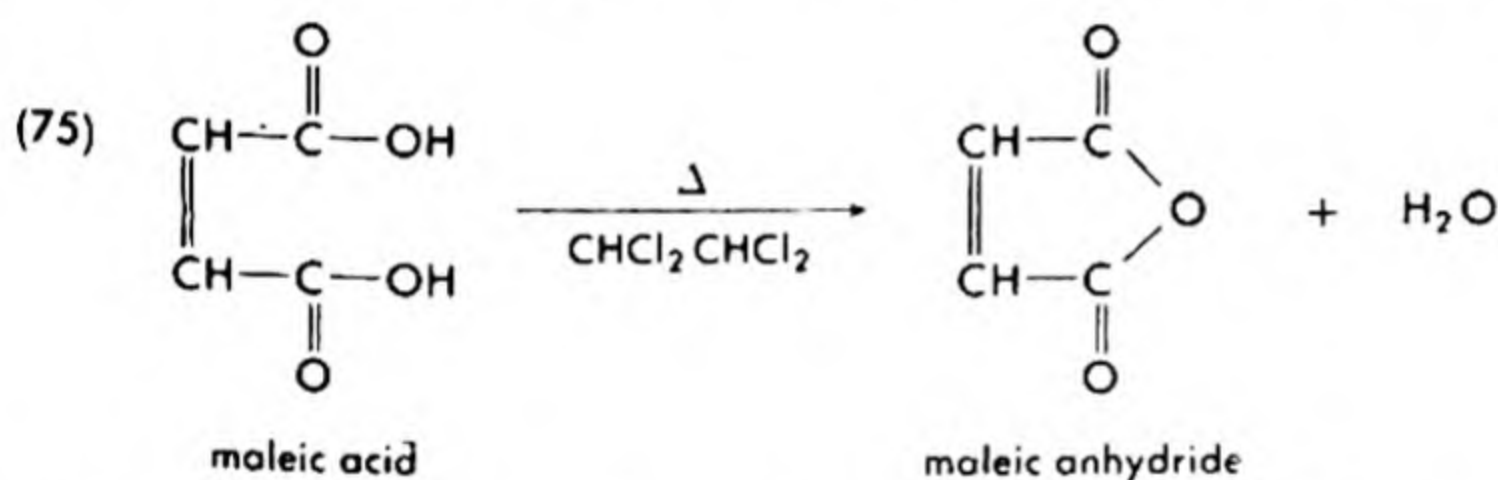
Cyclization reactions are so much more likely to occur than ordinary solvolysis that attempts at acylation of γ - or δ -substituted acids usually produce the cyclic products rather than the anticipated acylations; compare eqs. (73) and (74).



but



Cyclic anhydrides are also more easily formed and less reactive than open-chain anhydrides. Simply heating the dicarboxylic acid often forms the anhydride when a five- or six-membered ring is formed. Maleic anhydride is produced in 90% yield by azeotropic distillation of the water evolved with tetrachloroethane (eq. 75). When more direct methods fail, treatment of dicarboxylic acid with thionyl chloride generally brings



about cyclic anhydride formation. Rings larger and smaller than five and six atoms are not so readily formed. Thus, with adipic acid, a polymeric anhydride is formed.

In unsaturated systems and in many cyclic systems, fixation of carboxyl groups in *trans* positions prevents anhydride formation. The difficulty with which fumaric acid forms maleic anhydride is a classical example.

Cyclic imides are also readily prepared. Phthalimide is obtained in a yield of 97% by heating phthalic anhydride with aqueous ammonia until the water is driven off.

17-4 SIDE REACTIONS

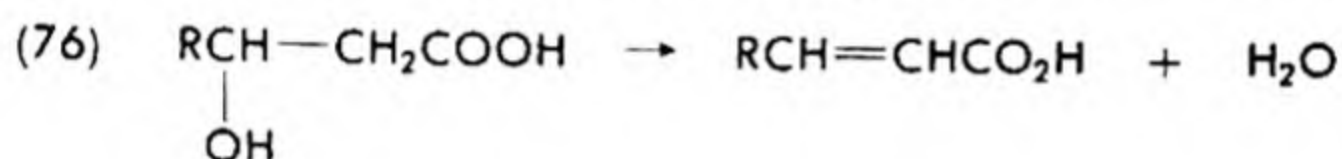
With the proper choice of conditions and a favorable equilibrium point, yields from solvolysis reactions of monofunctional compounds are generally excellent. Side reactions such as those between alcohols and hydrogen chloride or alcohols and sulfuric acid are so much slower than esterification or alcoholysis of amides as to be insignificant, provided steric

hindrance is absent and provided alkyl fragments that yield very stable carbonium ions are not involved. Esters of tertiary alcohols commonly react abnormally.

In some procedures water is introduced with the reagent, as in the use of aqueous ammonia or hydrazine hydrate. Hydrolysis in such instances becomes troublesome only when the reaction mixture is allowed to stand much longer than necessary, since the nitrogen bases are much more reactive than water.

Polyfunctional compounds can provide serious problems. Competition between different nucleophilic centers or different carbonyl groups, transesterifications, dehydrations, cyclizations, and addition to multiple bonds may occur.

In addition to the cyclizations mentioned in the preceding section, some other tendencies which may lead to products other than those expected should be mentioned. β -Hydroxy, amino, and mercapto acids which have α -hydrogen atoms have a strong inclination to eliminate water, ammonia, and hydrogen sulfide, respectively, to form 2-alkenoic acids (eq. 76).

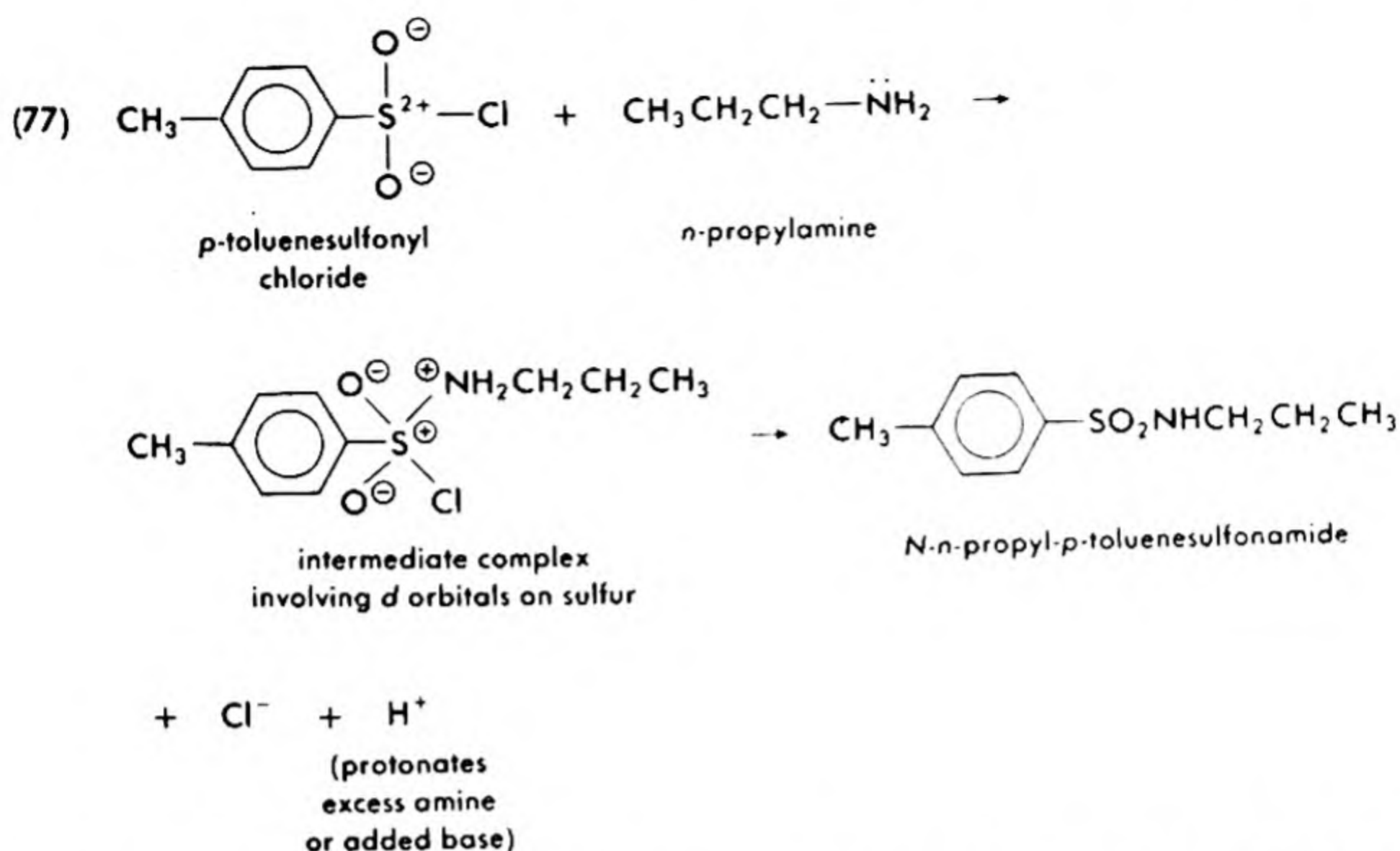


17.5 SOLVOLYSIS IN SULFONIC ACID DERIVATIVES

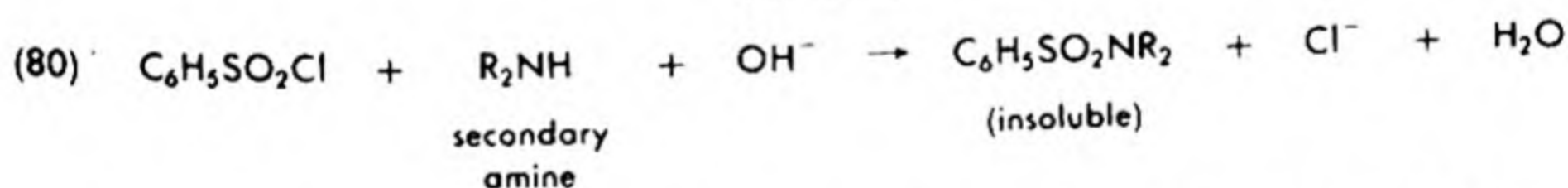
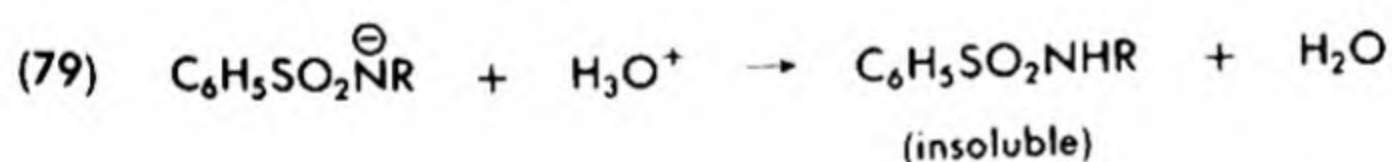
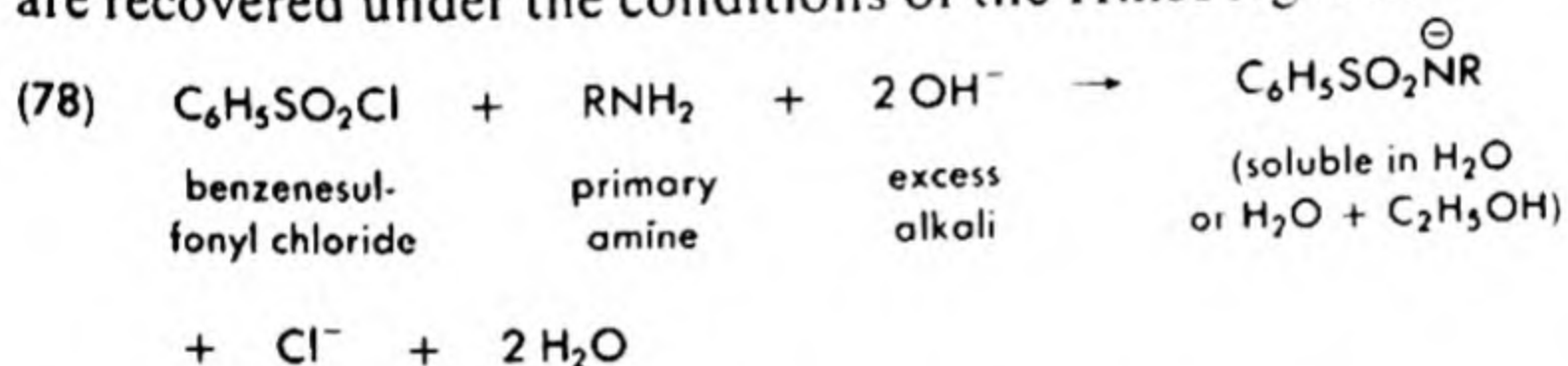
Some of the reactions of sulfonic acid derivatives bear formal resemblances to the reactions of carboxylic acid derivatives. The kind of unsaturation involved in the two cases differs, however; in the carboxylic acid derivatives, this was seen to break the π orbital of a carbon-heteroatom multiple bond in the addition step, (§17-1 and §17-2). Addition to the sulfur atom in a sulfonyl chloride, for example, probably involves instead the expansion of the sulfur valence sphere with the utilization of d AO's (eq. 77).

Such reactions can be used to prepare sulfonamides, as shown, from ammonia, primary amines, or secondary amines. They can also be utilized to prepare esters of sulfonic acids.

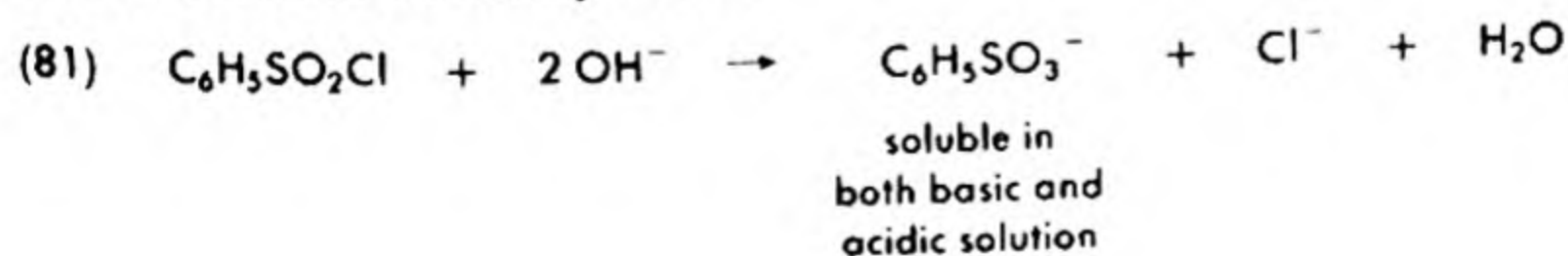
Sulfonamide formation from amines is utilized in a scheme for distinguishing primary, secondary, and tertiary amines, first used by and named after O. Hinsberg (1890). It may be recalled that the sulfonyl group has a strongly acidifying effect on the hydroxy group (§10-2G). The same factor causes sulfonamides with hydrogen on the nitrogen atom to be about as acidic as phenols. Thus, the sulfonamides of primary amines form sodium or potassium salts soluble in water or aqueous ethanol. Sulfonamides of secondary amines, which have no hydrogen on the amide nitrogen atom, do not form salts, hence do not dissolve. Ter-



tiary amines, which have no N—H bond, do not form sulfonamides and are recovered under the conditions of the Hinsberg test.



Since the sulfonyl halide also reacts with the alkali present, an excess must be used, and the excess must be destroyed by the alkali before the test results can be interpreted.



SUPPLEMENTARY READINGS

Gould, E. S., *Mechanism and Structure in Organic Chemistry*, Holt-Dryden, New York, 1959, Chapter 9.

Hine, J., Physical Organic Chemistry, 2nd Ed., McGraw-Hill, New York, 1962.
Chapter 12.

QUESTIONS AND PROBLEMS

1. Define or illustrate the following terms.

- | | |
|---------------------|------------|
| a. solvolysis | d. lactide |
| b. solvolytic agent | e. lactam |
| c. lactone | |

2. (A) Write the equations for the equilibria (actual or hypothetical) relating the following pairs of compounds. Use structural formulas. (B) Write an arrow over the equilibrium sign to indicate the direction in which equilibrium is normally more complete (20°, equivalent quantities of reagents, only those reagents present which are directly involved in the equilibrium). (C) Show how the reactions might be made to go to completion in the direction opposite to the normal, if this is possible. If not, write "irreversible."

- | | |
|---|---|
| a. ethyl acetate = acetamide | g. phthalic acid = phthalic anhydride |
| b. acetanilide = acetic anhydride | h. benzamide = benzoic acid |
| c. anhydride + hydrazine = maleic hydrazide | i. methyl salicylate = salicylic acid |
| d. urea + ethyl malonate = | j. δ -valerolactam = δ -aminovaleric acid |
| e. propionic acid + hydrogen chloride = | |
| f. isobutyryl chloride = isobutyranilide | |

3. Write equations for the preparation of the following compounds from the suitable acids or acid derivatives indicated and such other reagents as are needed. Use structural formulas and indicate essential conditions. State how each reaction can be driven virtually to completion.

- | | |
|---|---|
| a. <i>n</i> -amyl <i>n</i> -caprate from acid and alcohol | d. β -naphthoamide from acid and urea |
| b. pivalanilide from acid and amine | e. pyruvitrile from acetic acid |
| c. phenylacetic acid from nitrile | |

4. Write equations for those of the following reactions that can be driven essentially to completion. Use structural formulas and indicate conditions necessary to favor the reaction.

- | | |
|---|---|
| a. ethanoic acid and ethanol | g. succinic anhydride and ammonia |
| b. butanoic acid and <i>p</i> -toluidine | h. ethyl 4-chlorobutanoate and ammonia |
| c. <i>n</i> -amyl propionate and water | i. α -butyrolactide and water |
| d. benzamide and sodium hydroxide | j. methyl benzoate and hydrazine |
| e. <i>n</i> -valeric acid and hydrogen chloride | k. methylaniline, benzenesulfonyl chloride, and dilute sodium hydroxide |
| f. acetanilide and ethanol | |

- l. methylammonium chloride, *p*-toluenesulfonyl chloride, and excess dilute sodium hydroxide
- m. dimethylaniline, *p*-bromobenzenesulfonyl chloride, and dilute sodium hydroxide

5. Outline a satisfactory method of preparing *p*-bromoaniline from benzene involving a protected amino group.

6. Show how the following syntheses can be performed in acceptable yield. Indicate reagents and essential conditions. Use structural formulas for organic compounds.

a. lactide from propylene

b. cyclohexylamine from cyclohexanecarboxylic acid

c. parabanic acid, or oxalylurea, from oxalic acid, ethanol, and phosgene

7. Write equations for the reactions that occur between propionic acid and *n*-hexylamine at 25° and at 140°. Draw the energy diagrams for the two processes (noting that a proton transfer is a single-step process). Explain the difference in products at the different temperatures.



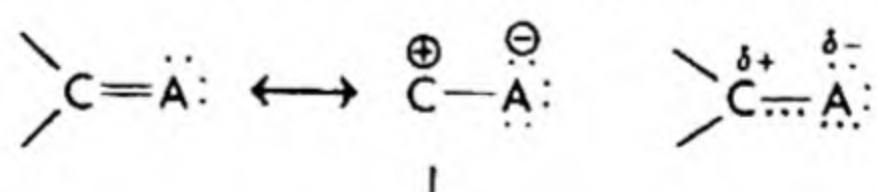
Nucleophilic Additions and Displacements at Unsaturated Atoms

II. Reactions of Aldehydes, Ketones, and Nitriles

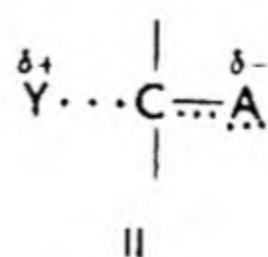
18-1 GENERAL MECHANISMS FOR NUCLEOPHILIC ADDITION

The reaction type considered in this chapter is that characteristic of functional groups such as carbonyl, $C=O$, and nitrile, $-C\equiv N$, which have a multiple bond between a carbon atom and another atom with greater electron affinity. Such bonds are significantly different from most carbon-carbon bonds, being polarized in the ground state, I, such that the carbon atom has a partial positive charge and the heteroatom has a partial negative charge. The bond is also highly polarizable, so that attack on the carbon by a nucleophile gives a transition state, II, in which the negative charge is located on an atom of high electron affinity.

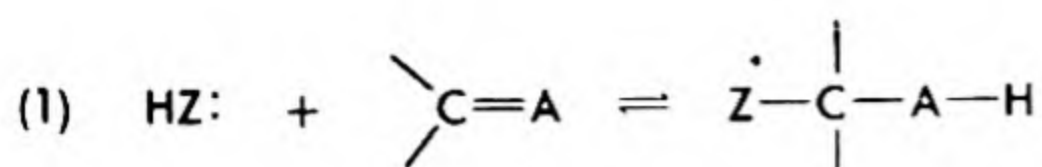
Valence-bond structures and hybrid structure of a polar unsaturated bond:



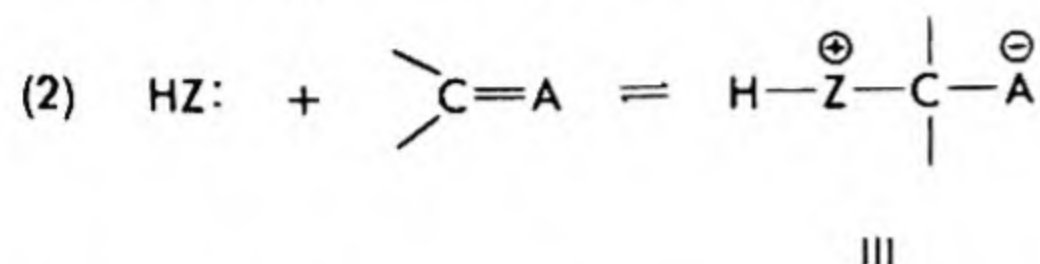
Transition state for attack of Y^- on $C=A$:



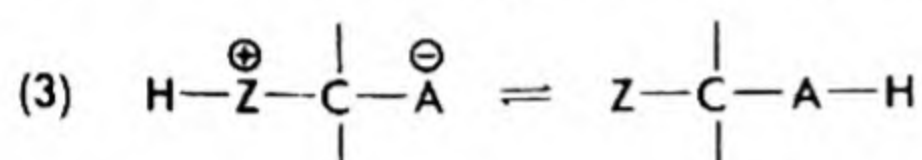
The addition of a molecule, HZ , to a polar multiple bond, $\begin{array}{c} \diagup \\ \diagdown \end{array} C=A$ is represented in eq. (1). Mechanistically, one may assume that the first step



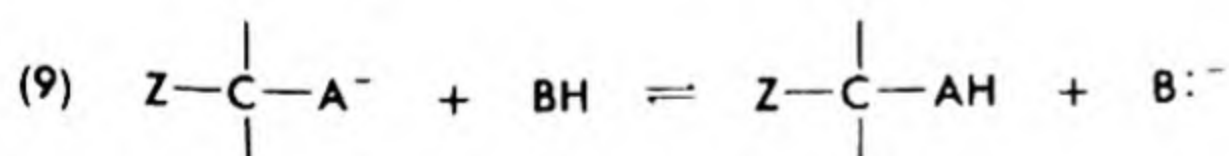
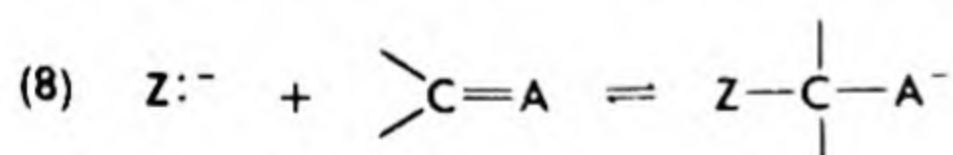
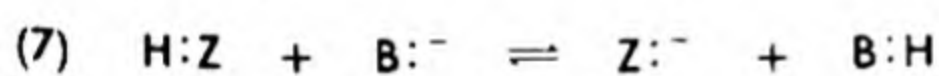
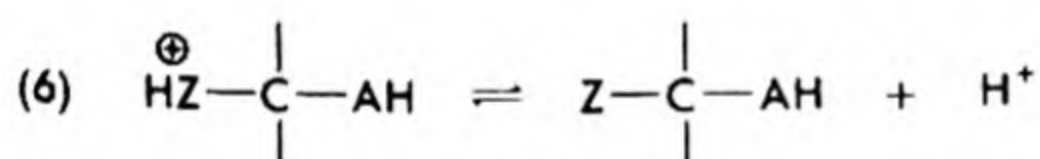
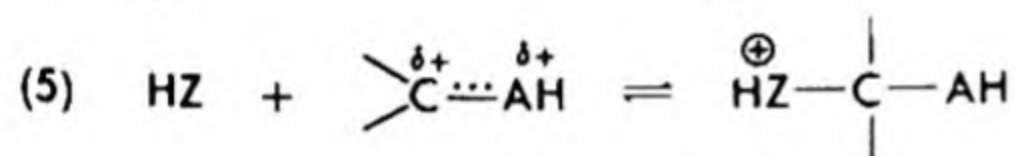
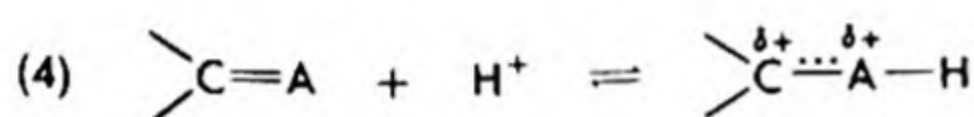
in the *uncatalyzed* reaction involves attack by the nucleophile, HZ, on the carbon atom, as in eq. (2), to give the dipolar molecule, III, followed by



proton transfers, represented by eq. (3), to give the product. One might



anticipate that acid- and base-catalyzed mechanisms would be readily available to such a system. This in fact is the case. The acid-catalyzed reaction may be formulated as in eqs. (4), (5), and (6) while the base-catalyzed reaction is given in eqs. (7), (8), and (9). The situation is pre-

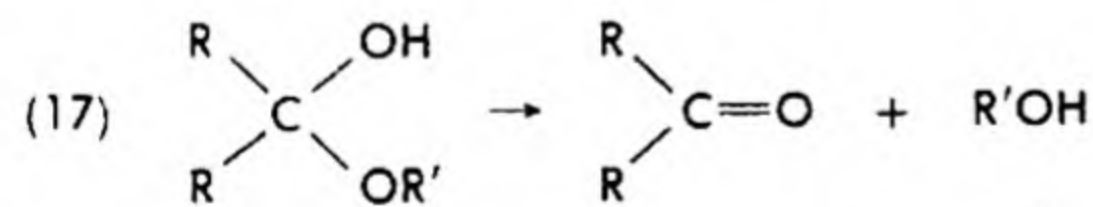
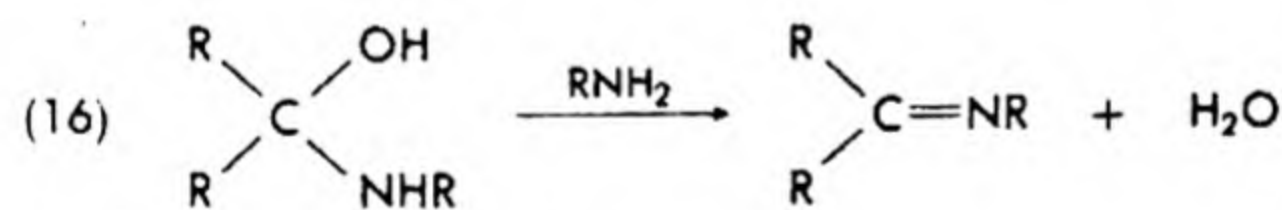
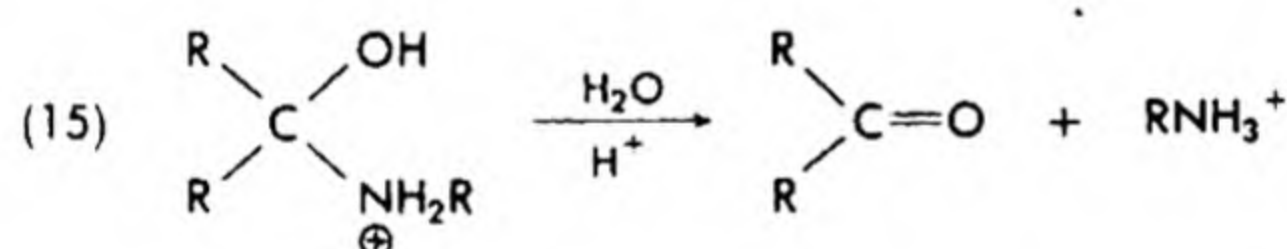
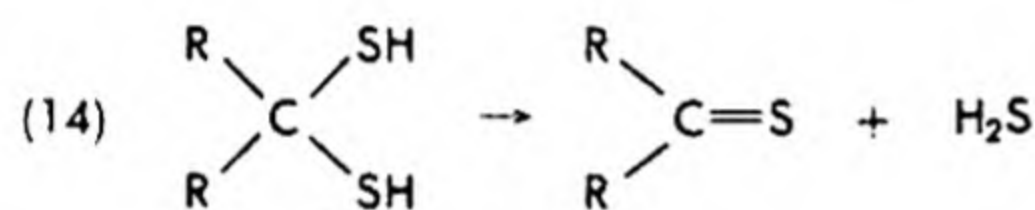
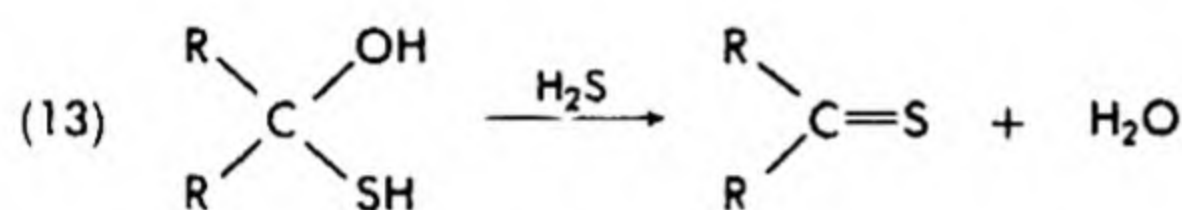
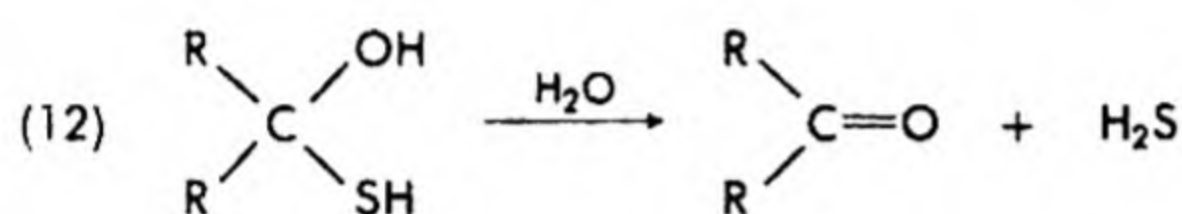
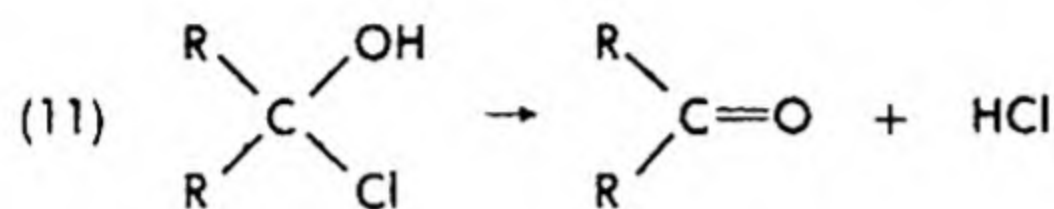
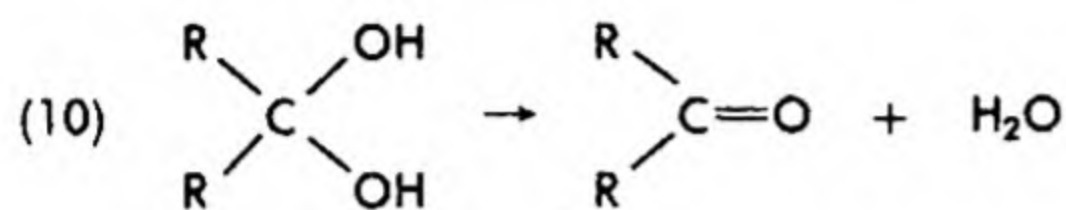


cisely analogous to those already discussed in the previous chapter (§17-3A and §17-3B). Acid catalysis is effective in making the unsaturated compound more reactive and base catalysis by increasing the strength of the nucleophile.

A. Reversibility of Reactions and Stabilities of Adducts

One should note that the formation of addition complexes is reversible. The position of equilibrium varies with conditions and, as might be anticipated, depends markedly on the nature of HZ and of the unsaturated compound. In many cases, the addition products are quite unstable and

appear only as intermediates in reaction sequences. Included among chemical species that are only rarely stable enough to isolate are *gem*-diols (eq. 10), *gem*-halohydrins (eq. 11), *gem*-hydroxythiols (eqs. 12 and 13), *gem*-dithiols (eq. 14), *gem*-hydroxyamines (eqs. 15 and 16), and hemiacetals (eq. 17).



QUESTIONS AND PROBLEMS

1. List the classes of compounds studied in Unit II which contain functional groups of the type $\text{R}-\underset{\text{b}}{\overset{\parallel}{\text{C}}}-\text{y}$.

2. In any reaction involving a functional group of the type $\text{R}-\underset{\text{b}}{\overset{\parallel}{\text{C}}}-\text{y}$ what are possible first steps? Explain on the basis of forces in the molecule.

3. Point out the atom most likely to be attacked by a nucleophile in each of the following compounds. Write the formula for the first intermediate in the reaction of each compound with ammonia.

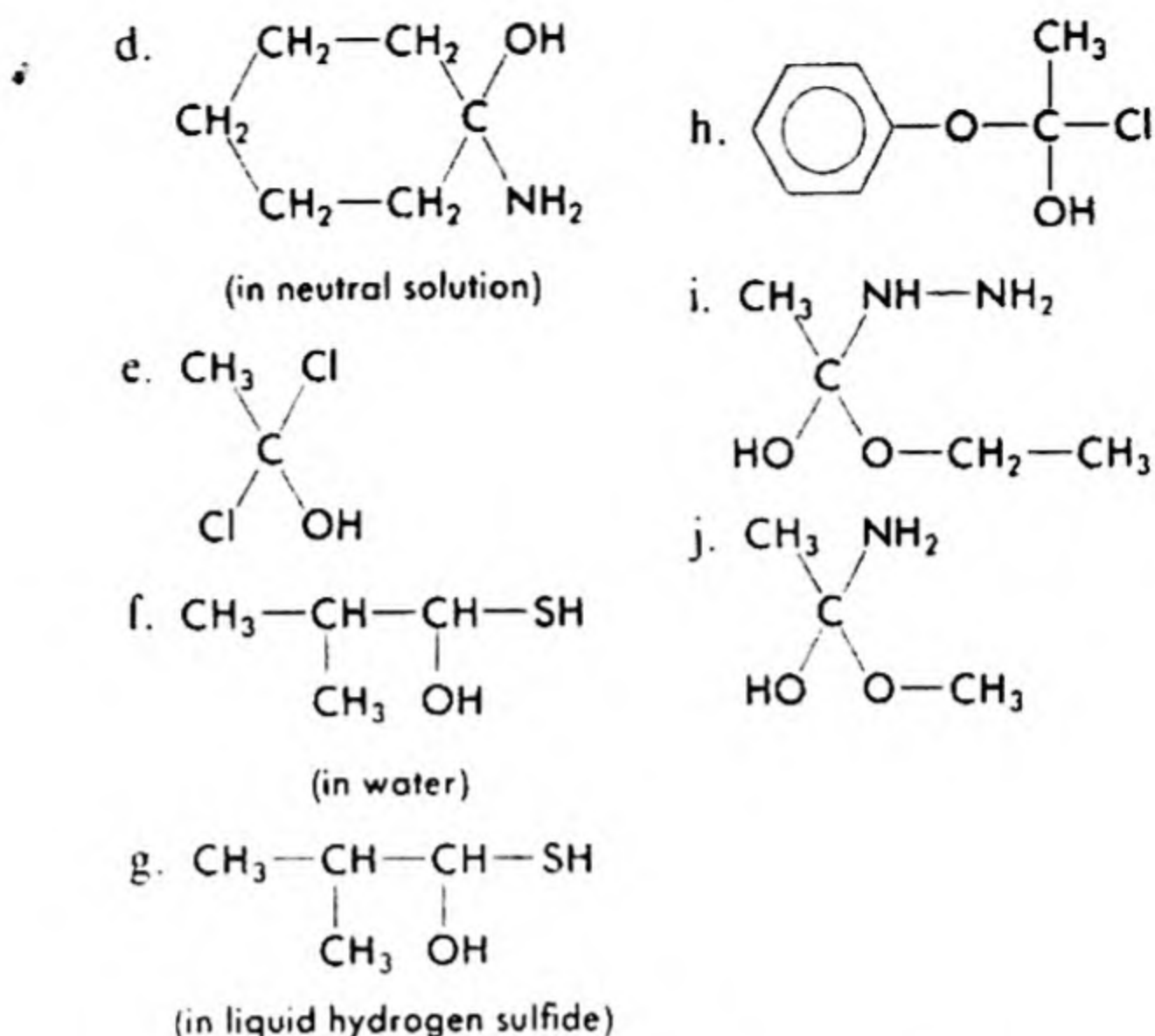
- | | |
|------------------------|--|
| a. acetaldehyde | e. ketene, $\text{CH}_2=\text{C}=\text{O}$ |
| b. benzoyl chloride | f. ethyl acetoacetate, ethyl 3-keto- |
| c. methyl ethyl ketone | butanoate |
| d. butyronitrile | |

4. Write the structural formulas of the products to be expected when the following structures are initially formed. If the structure is already stable, write it and the word "stable."

- | | |
|--|---|
| a. $\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{HO} \quad \text{OH} \end{array}$ | h. $\begin{array}{c} \text{CH}_2-\text{CH}_2-\text{Cl} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3 \end{array}$ |
| b. $\begin{array}{c} \text{C}_6\text{H}_5 \quad \text{OH} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{HO} \quad \text{OH} \end{array}$ | i. $\begin{array}{c} \text{CH}_3-\text{CH}-\text{SH} \\ \\ \text{SH} \end{array}$ |
| c. $\begin{array}{c} \text{HO}-\text{C}-\text{OH} \\ \\ \text{O} \end{array}$ | j. $\text{CH}_3-\text{CH}=\text{CH}-\text{OH}$ |
| d. $\text{CH}_3-\text{CH}_2-\underset{\text{Cl}}{\text{CH}}-\text{OH}$ | k. $\begin{array}{c} \text{CH}_3-\text{CH}=\text{C}-\text{O}-\text{CH}-\text{CH}_3 \\ \quad \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$ |
| e. $\text{CH}_3-\text{CH}_2-\underset{\text{Cl}}{\text{CH}}-\text{Cl}$ | l. $\begin{array}{c} \text{C}_6\text{H}_5-\text{CH}-\text{NH}-\text{CH}_2-\text{CH}_3 \\ \\ \text{OH} \end{array}$ |
| f. $\begin{array}{c} \text{C}_6\text{H}_5 \quad \text{OH} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_5 \quad \text{O}-\text{CH}_2-\text{CH}_3 \end{array}$ | m. $\begin{array}{c} \text{CH}_3 \quad \text{NH}-\text{OH} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{CH}_3 \quad \text{OH} \end{array}$ |
| g. $\begin{array}{c} \text{C}_2\text{H}_5 \quad \text{O}-\text{C}_2\text{H}_5 \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{C}_2\text{H}_5 \quad \text{O}-\text{C}_2\text{H}_5 \end{array}$ | n. $\begin{array}{c} \text{C}_6\text{H}_5 \quad \text{NH}-\text{NH}_2 \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{CH}_3 \quad \text{OH} \end{array}$ |
| | o. $\begin{array}{c} \text{C}_2\text{H}_5-\text{CH}-\text{OH} \\ \\ \text{NH}-\text{NH}-\text{C}_6\text{H}_5 \end{array}$ |

5. Write equations showing what probably would be formed from the following unstable intermediates.

- | | |
|--|--|
| a. $\begin{array}{c} \text{CH}_3 \quad \text{OH} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{HO} \quad \text{CH}_2-\text{CH}_3 \end{array}$ | c. $\begin{array}{c} \text{CH}_2-\text{CH}_2-\text{OH} \\ \diagdown \quad \diagup \\ \text{C} \\ \diagup \quad \diagdown \\ \text{CH}_2-\text{CH}_2-\text{NH}_2 \end{array}$
(in acidic solution) |
| b. $\begin{array}{c} \text{Cl} \\ \\ \text{C}-\text{CH}_3 \\ \\ \text{SH} \end{array}$ | |



18-2 ADDITION PRODUCTS OF ALDEHYDES, KETONES, AND NITRILES

Certain substances form stable adducts at carbon-heteroatom multiple bonds. It is with such formation of stable addition products that this section is concerned.

A. Addends

Water, ammonia, alcohols, hydrogen cyanide, and sodium bisulfite add reversibly to aldehydes and some ketones. In the cases of water and alcohols, the equilibrium point of the reaction is usually very far toward the side of the free carbonyl compound. However, in the alcohol addition, the addition product, a hemiacetal, is an intermediate in the formation of an acetal, which is a stable compound since it has no hydrogen atom in the correct position to be lost from the electron-attracting groups.

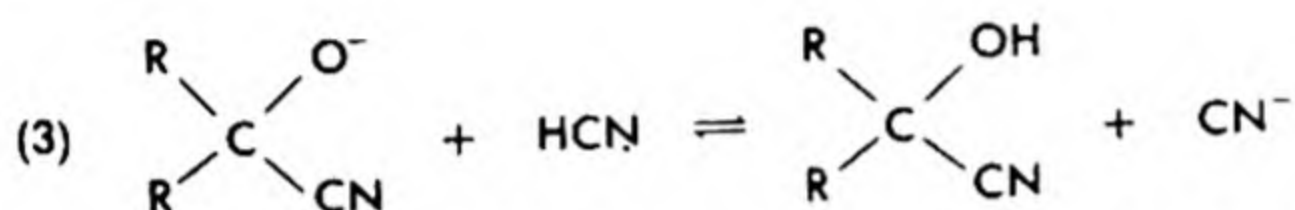
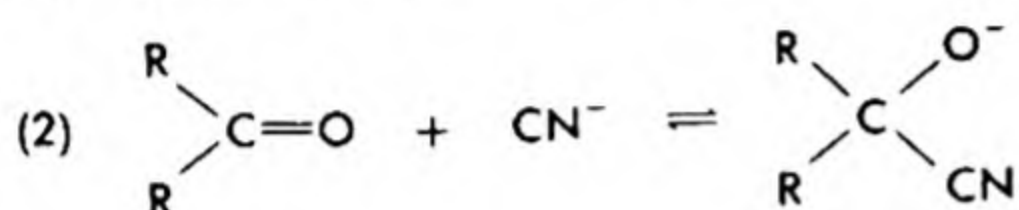
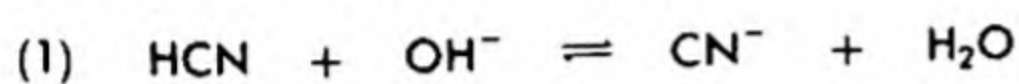
Reactions of ammonia and sodium bisulfite, though reversible, occur with sufficient completeness with aldehydes to form isolable products. Ketones with groups larger than methyl on the carbonyl group present a combination of steric and electronic factors which so slow down the formation of the bisulfite addition product that there is little yield within an hour. Major exceptions are cyclic ketones through cyclooctanone, in which the alkyl moiety on the carbonyl groups is pinned back out of the way by ring formation. Ketones also react with ammonia, but the reactions are not simple addition.

The addition of hydrogen cyanide to most aldehydes and ketones is complete enough for the cyanohydrin to be isolated. Cyanohydrins are intermediates in the syntheses of hydroxy acids and their derivatives,

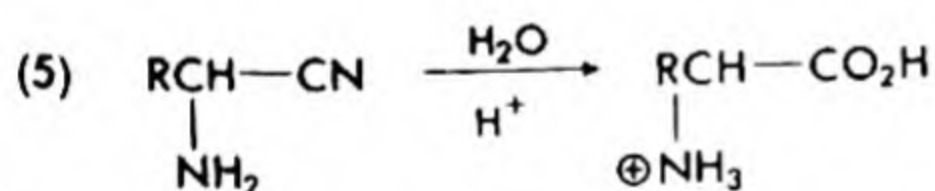
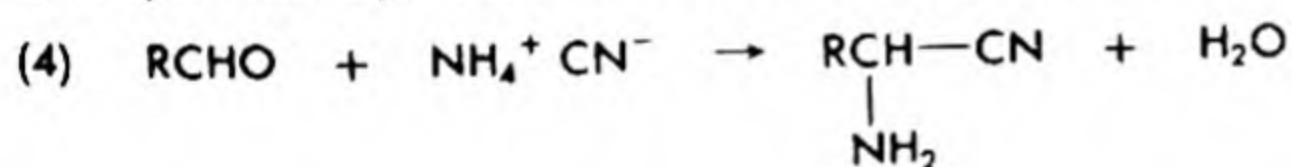
where the cyanohydrin is solvolyzed in acid solution. Addition of acetylenes to aldehydes and ketones also involves base catalysis.

B. Cyanohydrin Formation

The formation of aldehyde and ketone cyanohydrins does not proceed in acid solutions, but goes rapidly when small amounts of base are present. Thus, the cyanide ion is the required nucleophile and hydrogen cyanide is ineffective in attacking a carbonyl group. The steps shown in eqs. (1), (2), and (3) are involved.

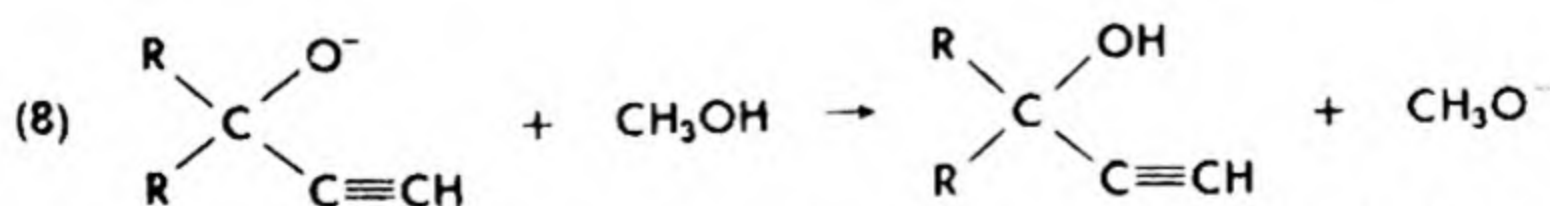
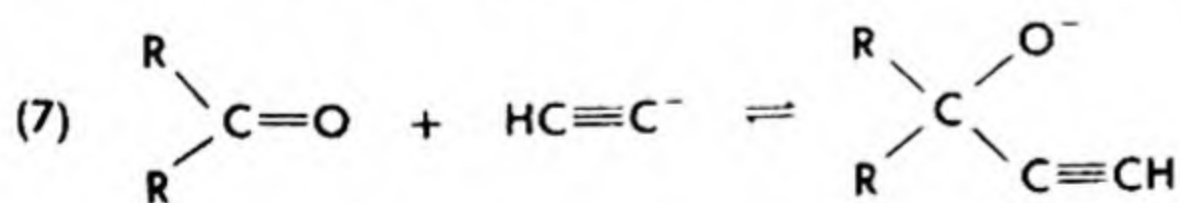


The lability of the hydroxyl group in the cyanohydrin is readily observed in that use of ammonium chloride and sodium cyanide gives an α -aminonitrile (eq. 4). Acid-catalyzed hydrolysis leads to an α -amino acid (outline 5). This is called the *Strecker synthesis*.

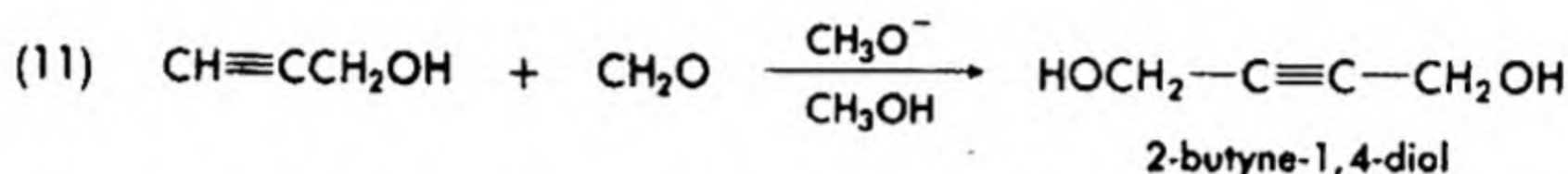
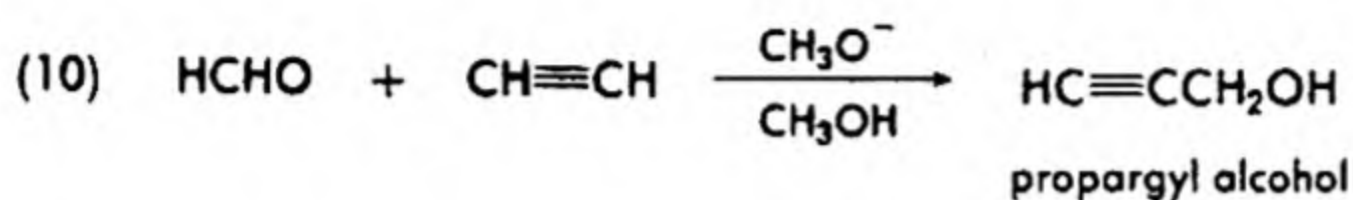
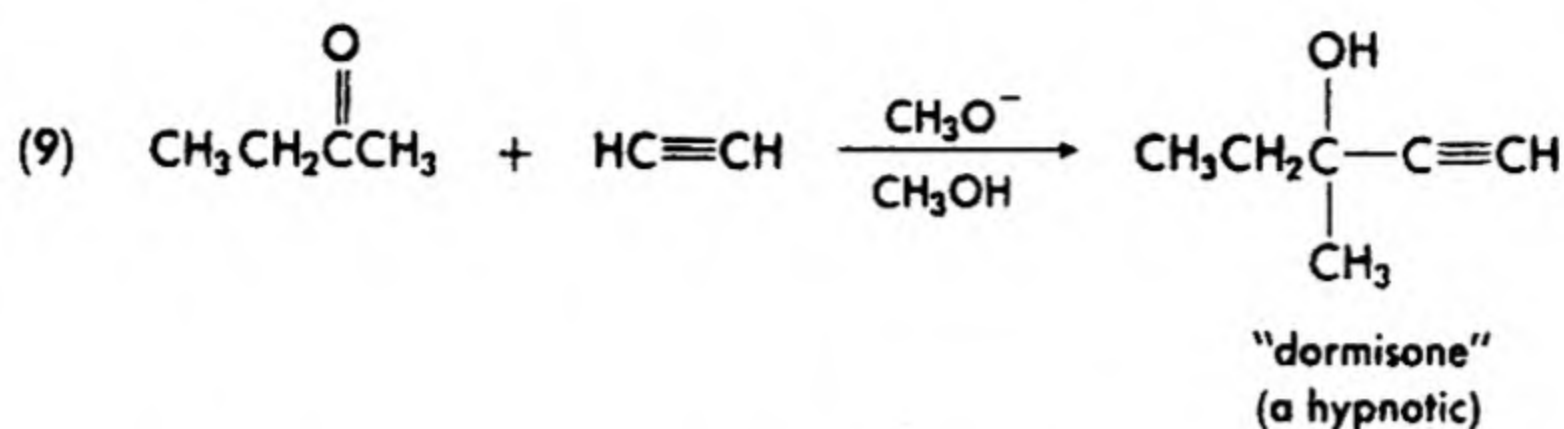


C. Reaction with Acetylene. Ethynylation

The reaction of acetylene with carbonyl compounds is catalyzed by bases and follows a similar mechanism (eqs. 6, 7, and 8). This reaction succeeds with aldehydes which do not have active hydrogen atoms and



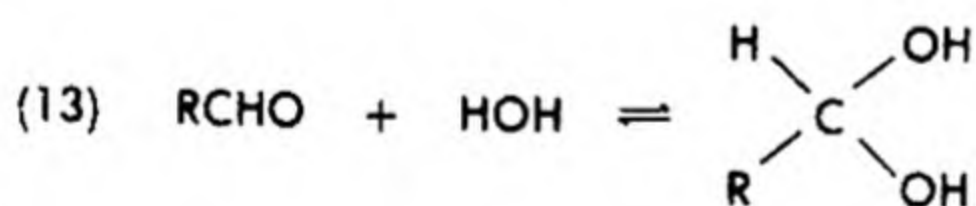
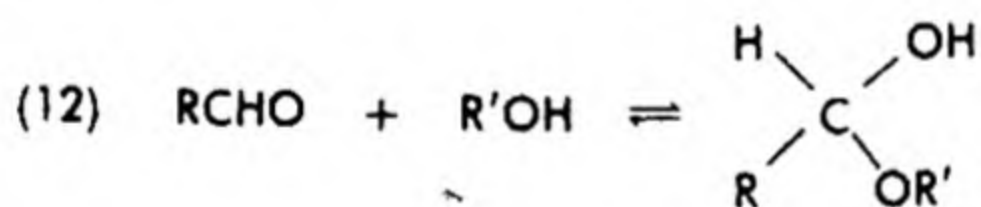
with ketones. It therefore represents a useful alcohol synthesis (eqs. 9, 10, and 11). The acetylenic alcohols can be hydrogenated to the corre-



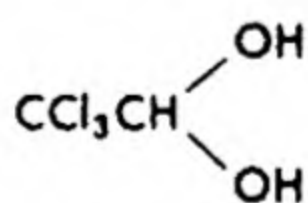
sponding allylic and saturated alcohols. The process of adding acetylene is called *ethynylation*.

D. Hydrate, Acetal and Hemiacetal Formation

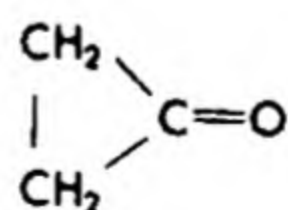
The formation of hemiacetals by addition of alcohols to aldehydes or ketones (eq. 12) ordinarily has the position of equilibrium well to the left, as does the hydration reaction shown in eq. (13). In general, these reactions are so unfavorable that, even in water or in alcohol solutions, the carbonyl compounds exist largely as such. A few



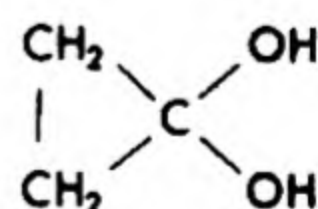
interesting exceptions may be mentioned. Trichloroacetaldehyde, or chloral, forms a very stable hydrate, chloral hydrate, which requires concentrated sulfuric acid to dehydrate it. It is a hypnotic, often called "knock-out drops." Cyclopropanone has never been prepared. All attempts to prepare it result in the hydrate.



chloral
hydrate



cyclopropanone

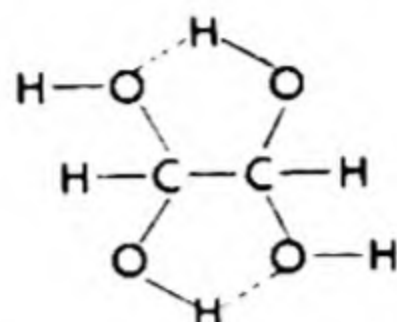


cyclopropanone
hydrate

This fact is rationalized by consideration of angle strain. The internal angles in a three-membered ring must average 60° ; thus, the angle strain in

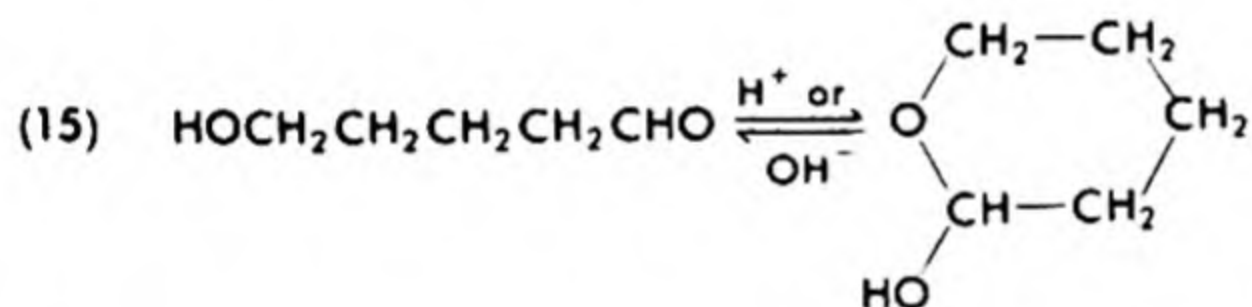
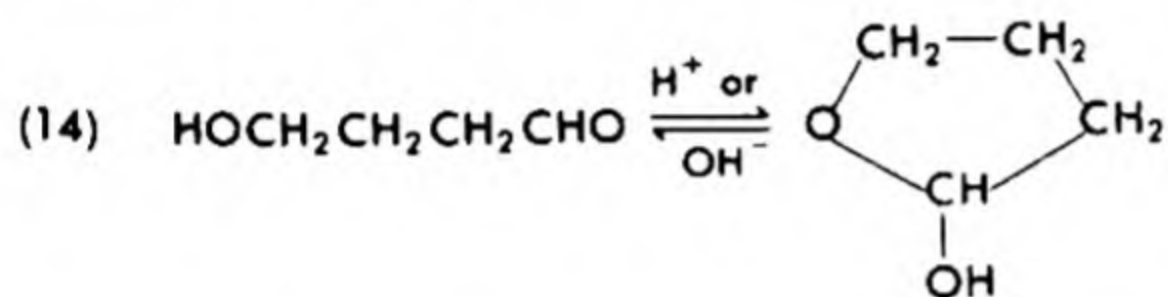
cyclopropanone at the trigonal carbon atom is 60° , whereas that of the hydrate at the corresponding (now tetrahedral) carbon atom is significantly less. These compounds also form stable hemiacetals.

Another stable hydrate is glyoxal dihydrate. In this, internal hydrogen bonding is considered to contribute significantly to its stability.



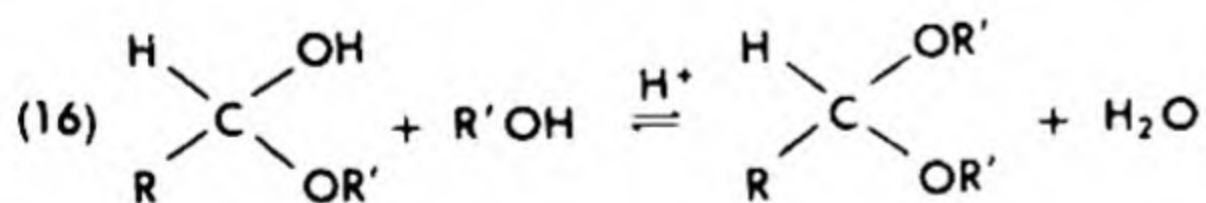
glyoxal dihydrate

Other cases where stable hemiacetals are observed are with γ - or δ -hydroxy carbonyl compounds, which form stable cyclic hemiacetals (called lactals) (eqs. 14 and 15). These are of particular importance in

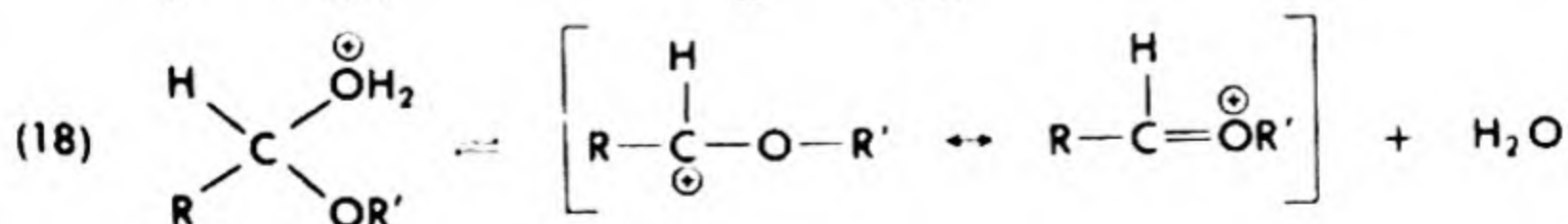
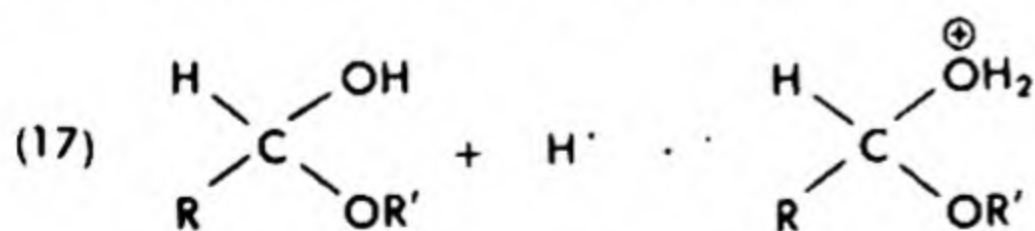


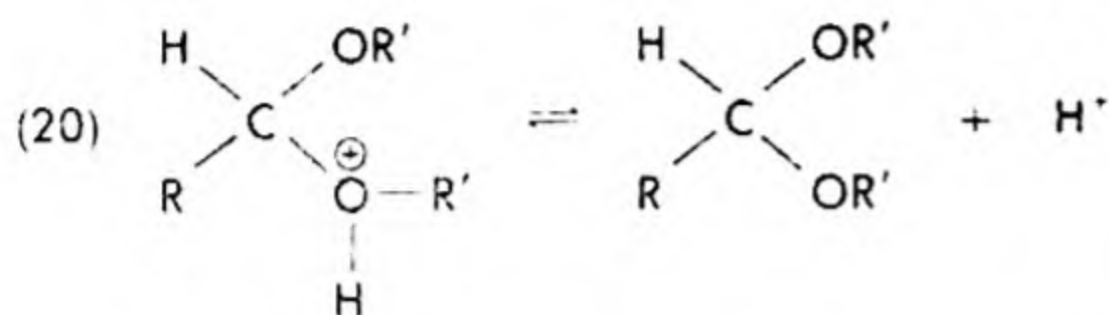
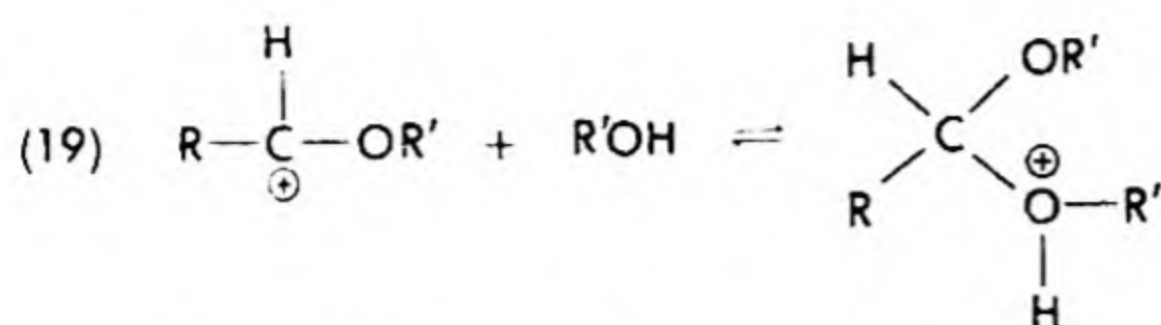
carbohydrate chemistry (§38-1B(5)). Acidic or basic catalysis is involved in such reactions.

The further reaction of a hemiacetal with excess alcohol to give an acetal is acid-catalyzed (eq. 16). These reactions involve carbonium ions,



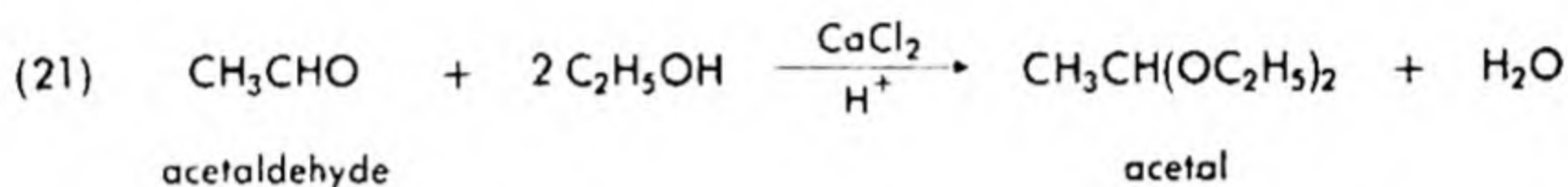
which are greatly stabilized by the α -alkoxy group (eqs. 17-20). As this mechanism is related to standard ether formation and hydrolysis mecha-



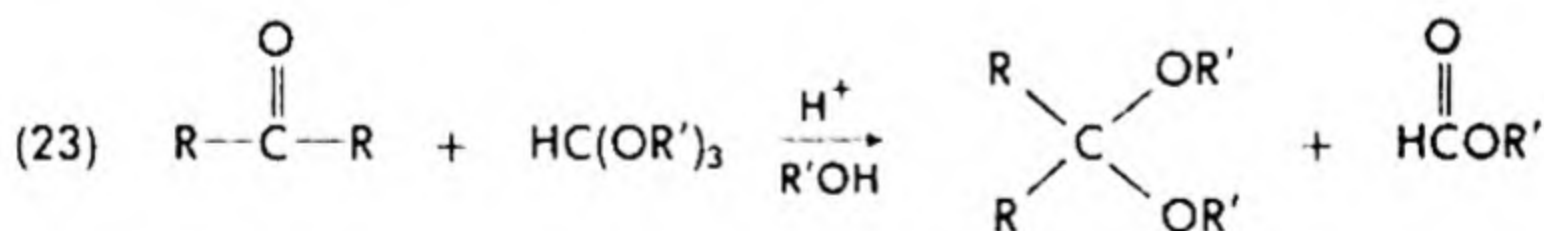
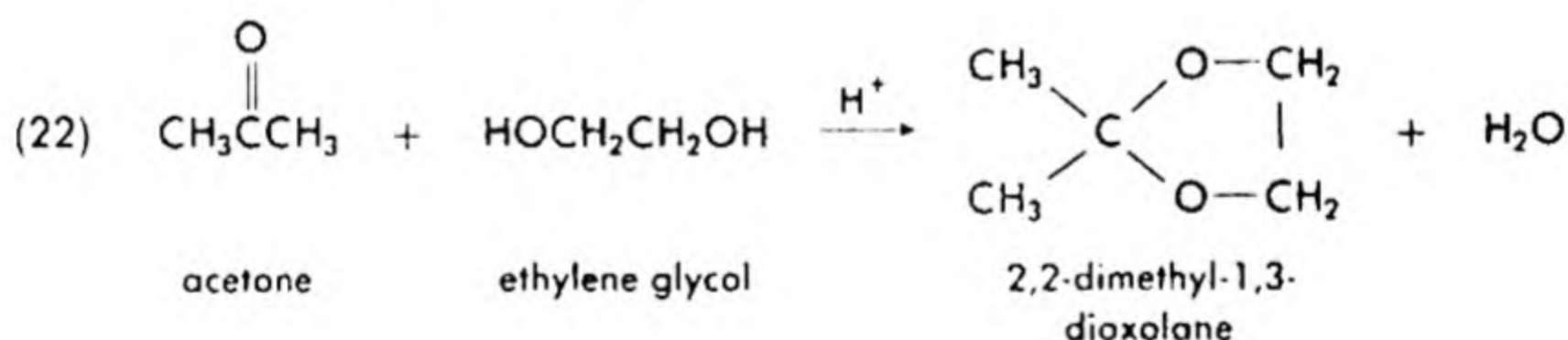


nisms, bases are not catalytically active. The formation of acetals is often the unfavorable direction in an equilibrium situation, so that such reactions are run in anhydrous alcohol solutions and water is removed by desiccation or by azeotropic distillation.

Acetal formation is exemplified by the preparation of diethylacetal (generally called "acetal") from acetaldehyde and ethyl alcohol (eq. 21). Ketones do not ordinarily form ketals under these conditions, because of



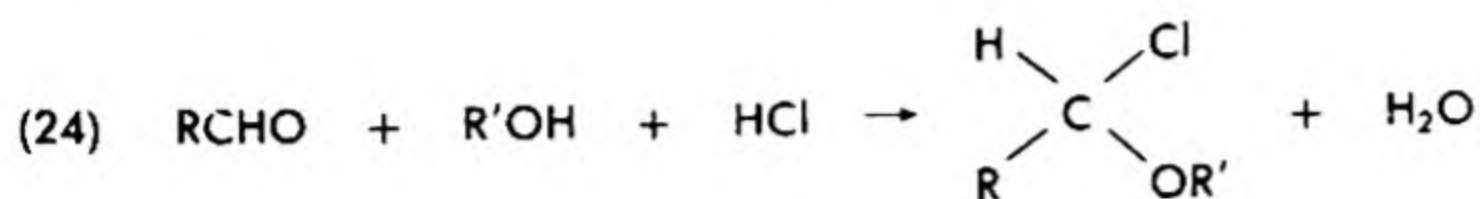
still less favorable equilibria, although cyclic ketals are readily formed from ketones and 1,2-diols. The reaction between acetone and ethylene glycol to form 2,2-dimethyldioxolane is an example (eq. 22). Ketals related to ethyl alcohol or to methyl alcohol can be prepared from ketones and orthoformate esters (eq. 23).



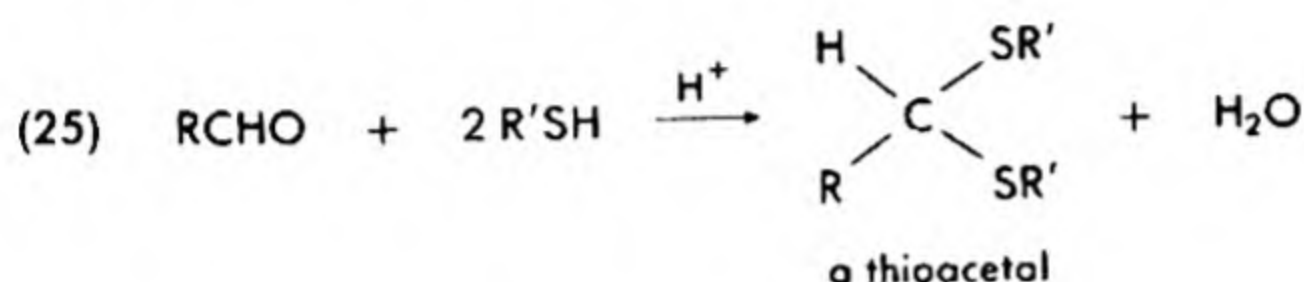
As acetals and ketals are stable in basic solution, while aldehydes and ketones undergo many base-catalyzed reactions, transformation of carbonyl compounds to acetals and ketals and subsequent regeneration of the carbonyl compound by acidic hydrolysis represents a way to protect the carbonyl function during reaction sequences.

When an excess of hydrogen halide is used in the treatment of an aldehyde with an alcohol, an α -halo ether results (eq. 24). This is a very

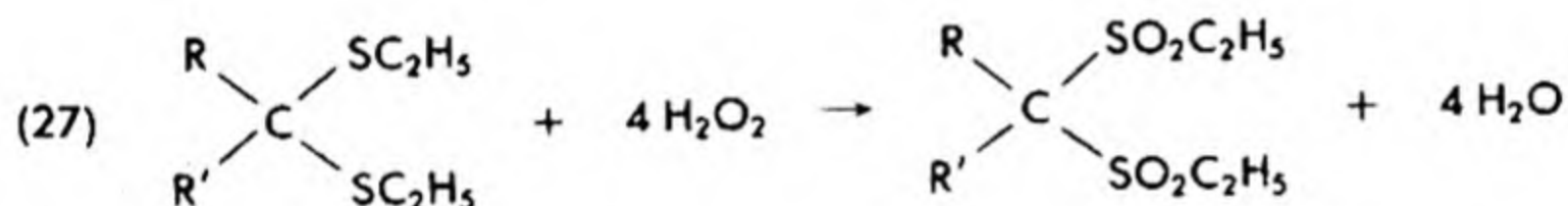
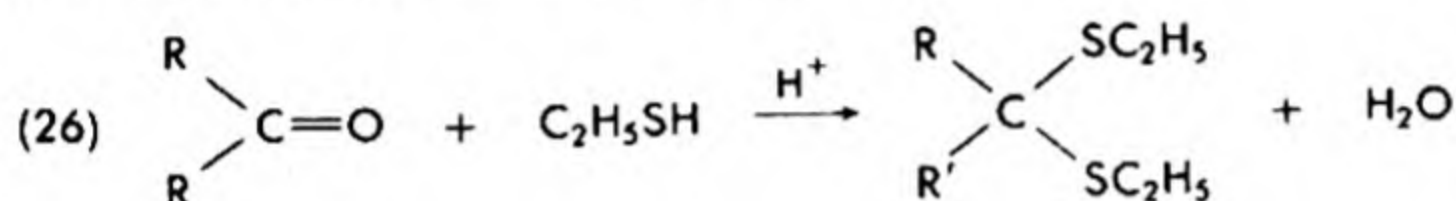
reactive class of compounds. Some of their reactions are considered in §19-5C.



Thioacetals are more stable than acetals, so that aldehydes and ketones react readily with mercaptans in the presence of acid catalysts (eq. 25). The formation of the hypnotics sulfonal and trional makes use of these



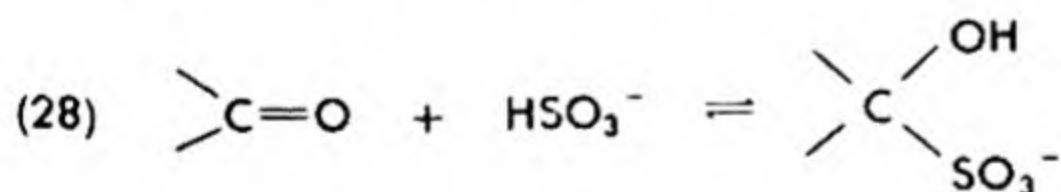
reactions, as shown in eqs. (26) and (27),



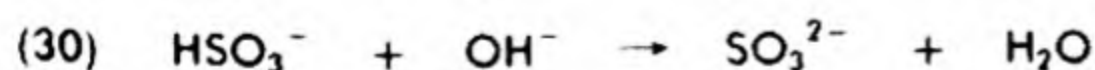
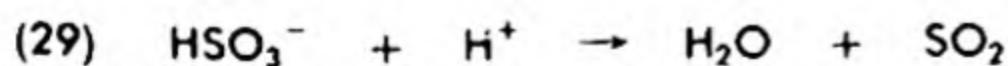
where $\text{R} = \text{R}' = \text{CH}_3$ for sulfonal and $\text{R} = \text{CH}_3$, $\text{R}' = \text{C}_2\text{H}_5$ for trional.

E. Bisulfite Addition Products

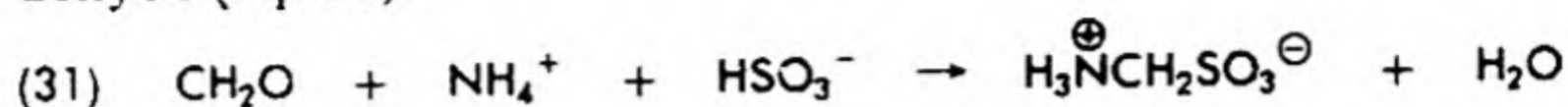
The reaction of aldehydes and ketones with sodium bisulfite follows the course shown in eq. (28). These bisulfite addition products are sodium



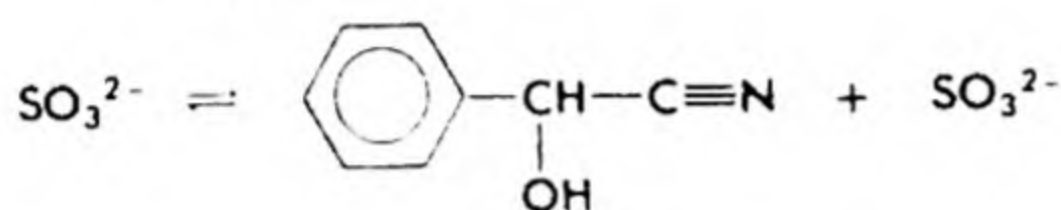
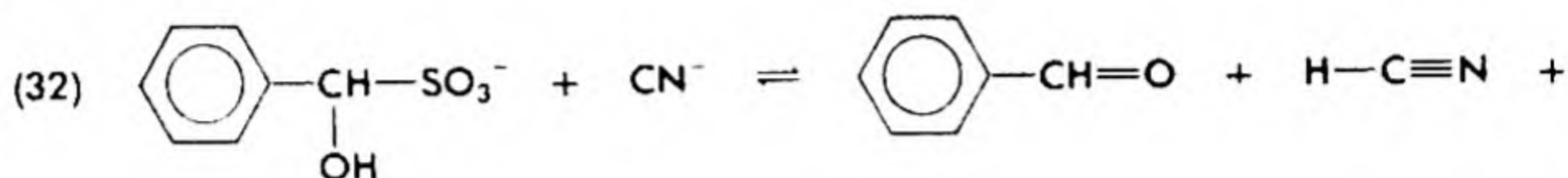
salts of α -hydroxyalkanesulfonic acids and are soluble in water, but insoluble in ethanol. They are used to separate aldehydes and methyl ketones (not aryl) from other neutral species by extraction into aqueous sodium bisulfite solutions or by precipitation from ethanol solutions. They are readily decomposed by acid or base, as the position of the equilibrium represented by eq. (28) is disturbed by the reactions depicted in eqs. (29) and (30).



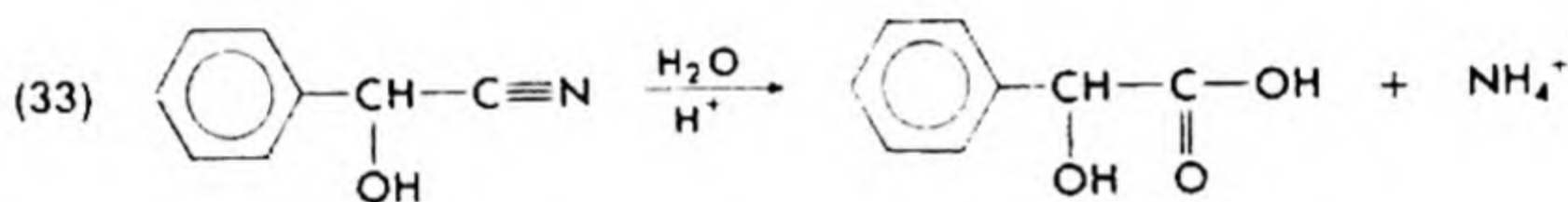
When ammonium bisulfite is used, the product of the reaction is the aminoalkanesulfonic acid. This is exemplified by the reaction of formaldehyde (eq. 31).



Another use of the bisulfite addition compound is as an intermediate in the synthesis of cyanohydrins. An alkali cyanide can be used instead of gaseous hydrogen cyanide. Using this technique, mandelic acid is readily prepared.



mandelonitrile

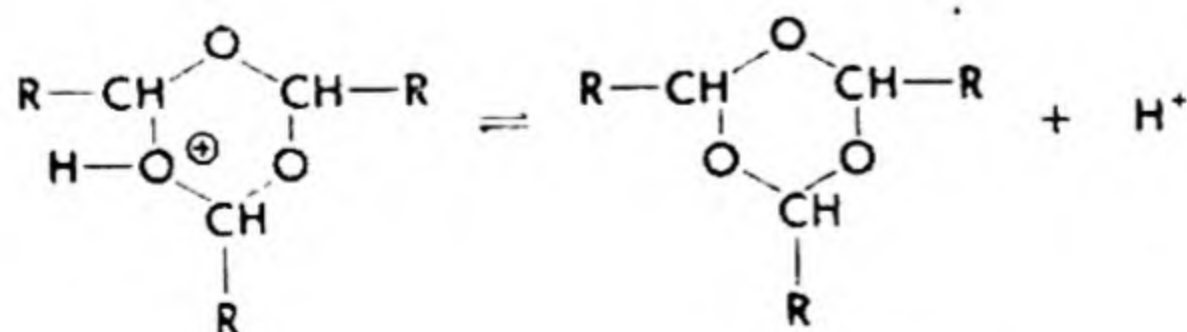
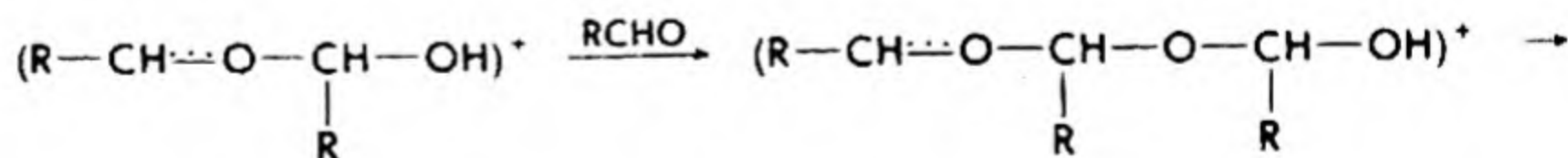


mandelic acid

F. Self-Addition 1,2 at the Carbonyl Group

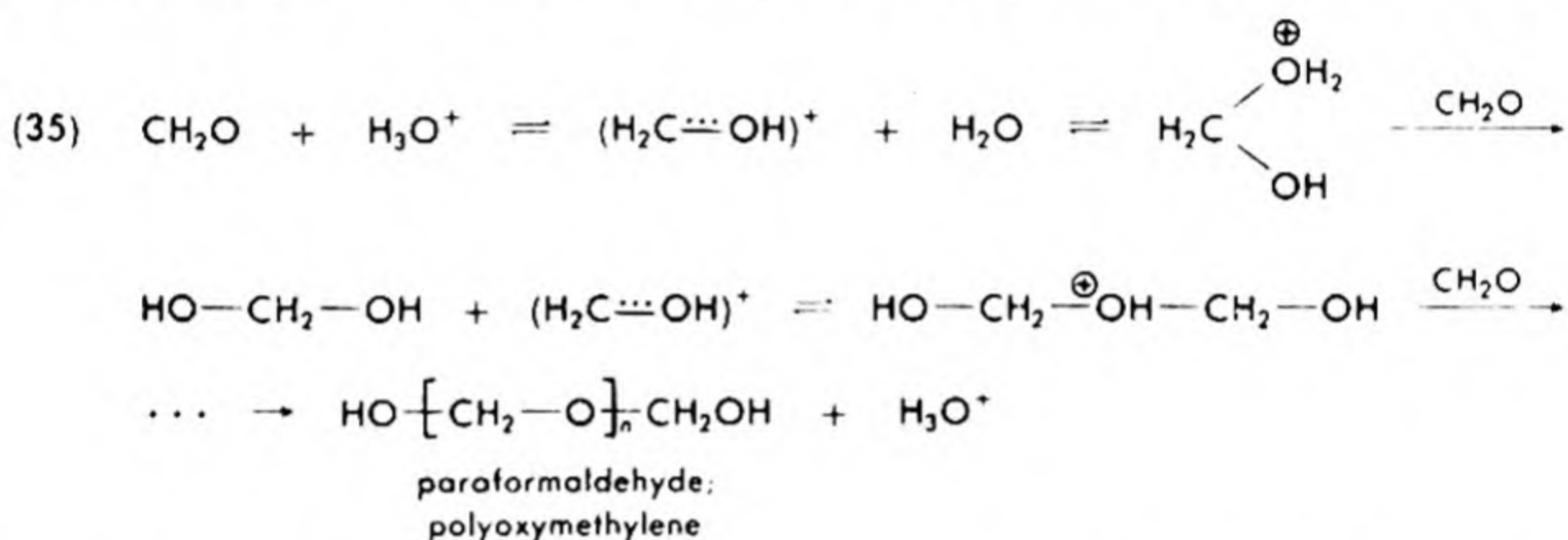
Self-addition (polymerization) of aldehydes occurs readily among the lower aliphatic homologs, especially formaldehyde. These reactions are reversible, hence the cyclic trimers or tetramers or the linear polymers can often be used in synthesis in place of the monomers when acid catalysis can provide the means of depolymerization.

In anhydrous acid media, both formaldehyde and acetaldehyde tend to cyclize, a process which may be represented as in outline (34).

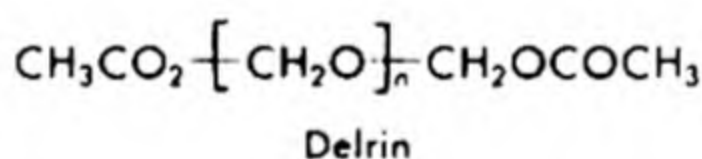
aldehyde
trimer

where $R = H$ or CH_3 . The product from formaldehyde is called trioxymethylene or *trioxane*; that from acetaldehyde, *paraldehyde*. Intervention of a fourth aldehyde molecule before cyclization produces a tetramer, etc.; a mixture of such oligomers of four to six units of acetaldehyde is called *metaldehyde*.

An alternative pathway is taken by formaldehyde in the presence of moisture. Addition of water forms the diol, formaldehyde hydrate, which then initiates a chain of hemiacetal formation (the inner linkages of which become acetal linkages). The reaction occurs slowly without acid, but is acid-catalyzed (outline 35). The product polyoxymethylene, when sta-



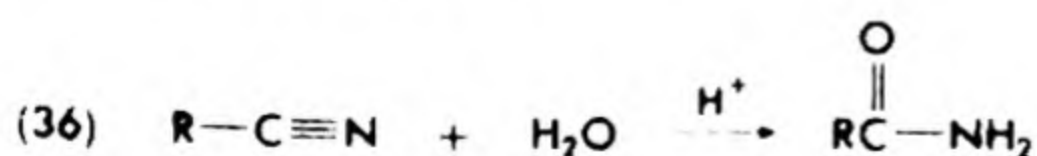
bilized by end-capping (reaction of the terminal hydroxy groups with acetic anhydride, §46-3G), forms a useful polymer, Delrin. Without the

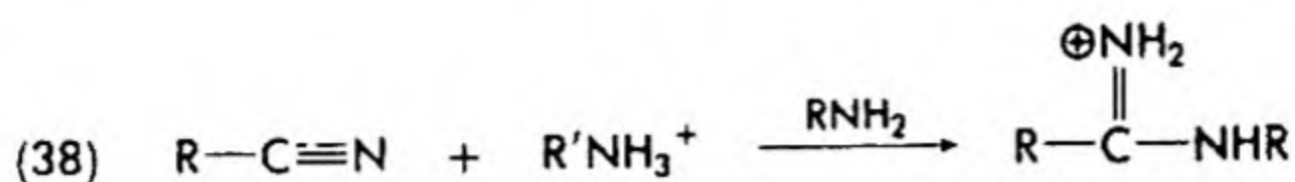


stabilization, paraformaldehyde has an appreciable equilibrium vapor pressure of formaldehyde, sufficient to make it slightly malodorous.

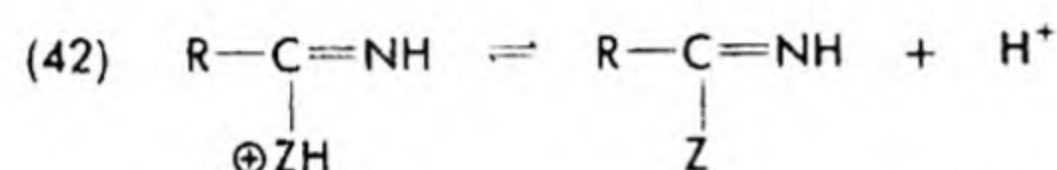
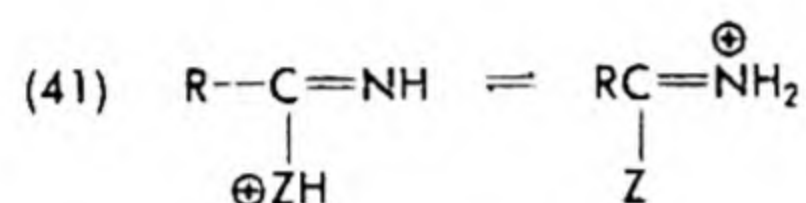
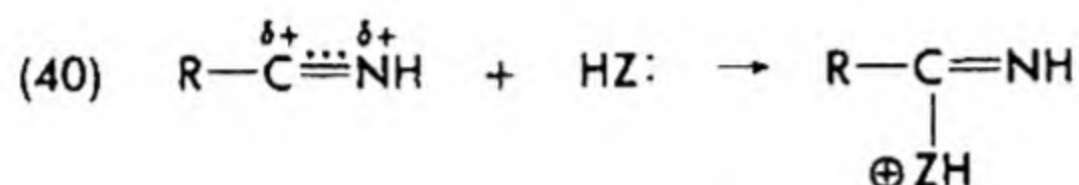
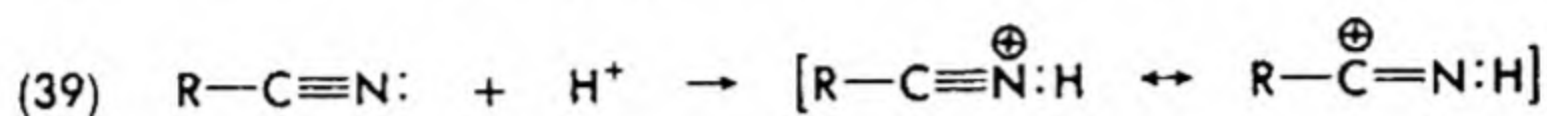
G. Addition to Nitriles

The carbon-nitrogen triple bond resembles the carbon-oxygen double bond in its susceptibility to acid- and base-catalyzed nucleophilic addition reactions. Here, addition of water to form amides (eq. 36), of alcohols to form imidates (commonly called imino esters) (eq. 37), or of ammonia and amines to form amidines (eq. 38) are very common. Acid catalysis is generally used. The basic imino esters and amidines are isolated as their salts (eqs. 37 and 38).

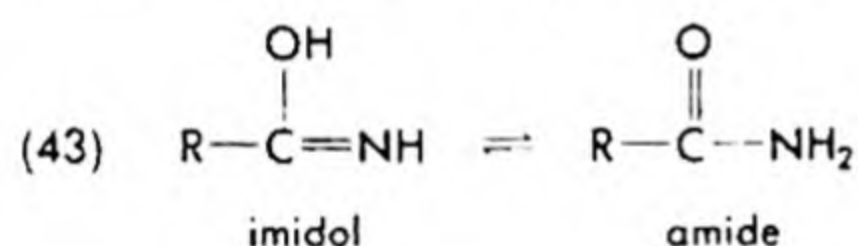




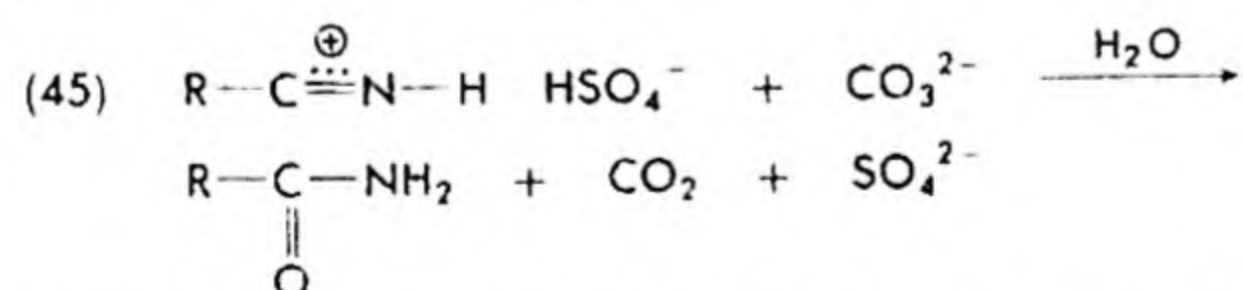
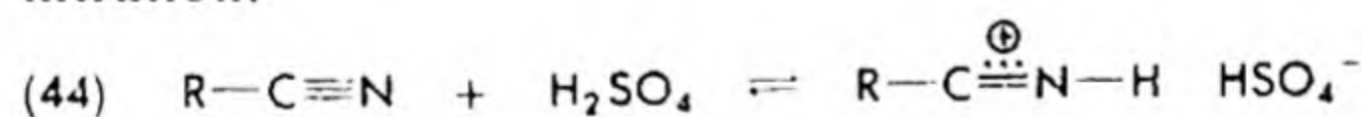
The acid-catalyzed reactions involve proton addition to the nitrogen atom (eq. 39), followed by attack of the nucleophile (eq. 40). Proton transfers then occur (eqs. 41 or 42). When water is added, the initial



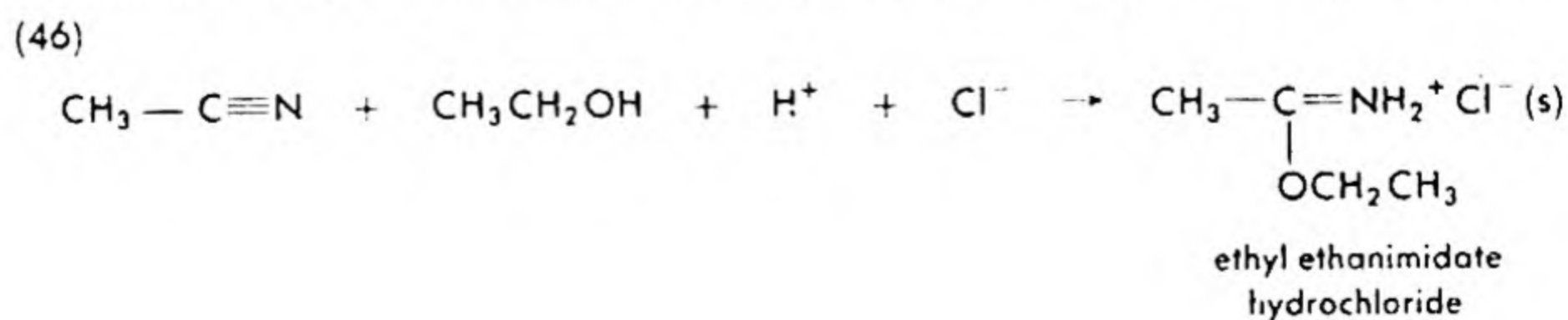
product is the *imidol*, which rapidly tautomerizes to the amide (eq. 43). As amides are readily hydrolyzed with mineral acid to acids and ammonium ion, special procedures have been developed to control the reac-

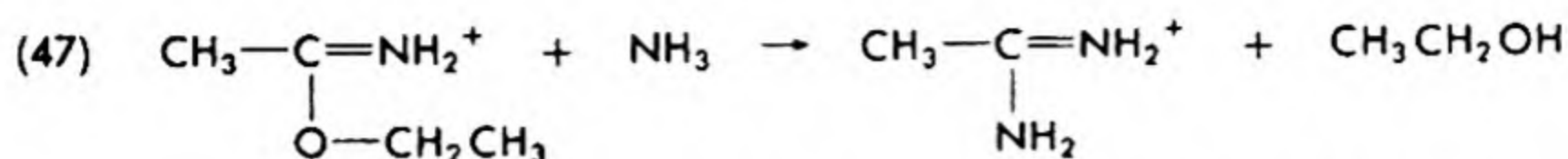


tion. One method that can be used is to add concentrated sulfuric acid to the nitrile, then treat it in an ice bath with sodium carbonate solution. The amide, if an insoluble solid, separates readily and is collected by filtration.



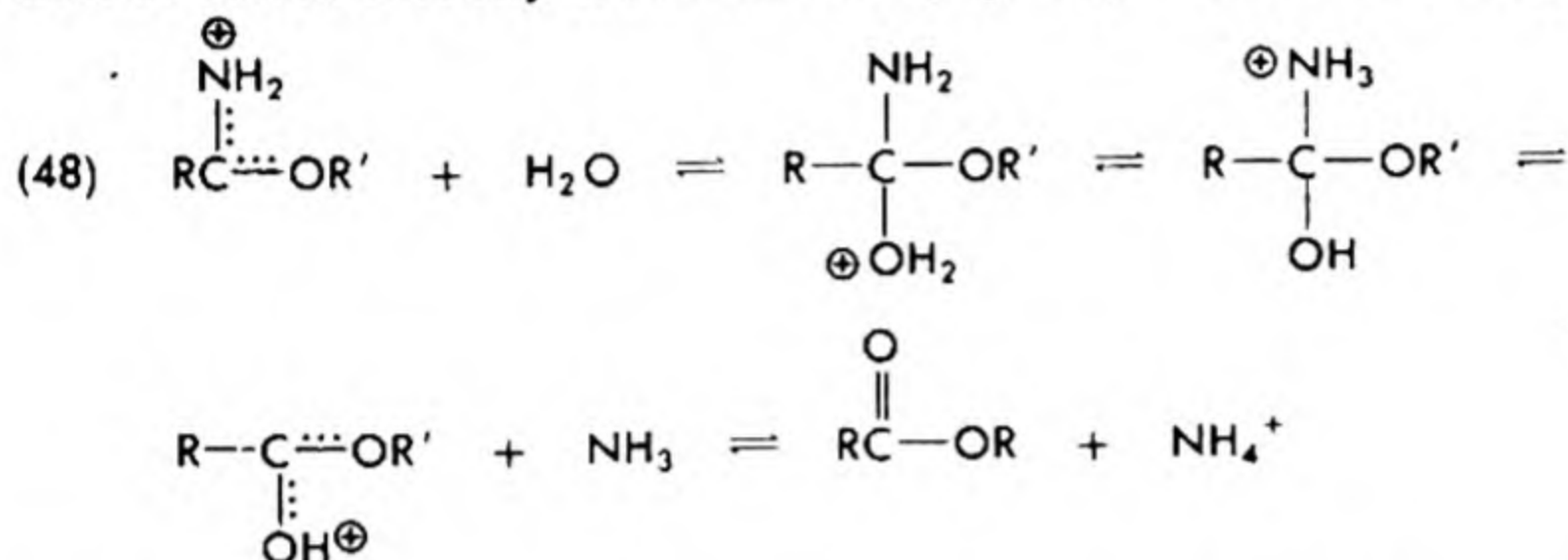
Formation of alkyl imidates (imino esters) readily stops at the addition of one molecule of alcohol, as long as water is rigidly excluded. Ethyl ethanimidate hydrochloride is readily obtainable (eq. 46). Conversion of



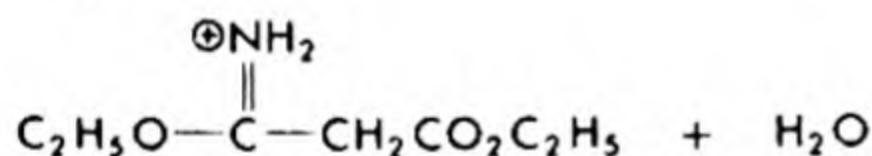
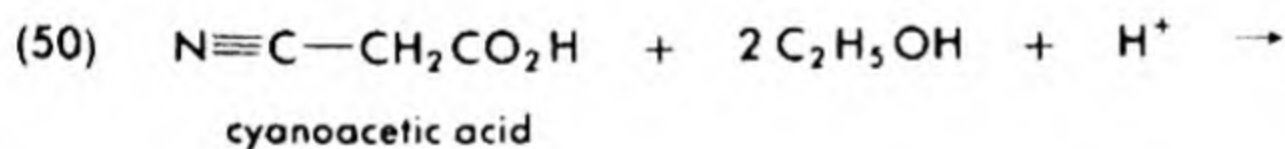
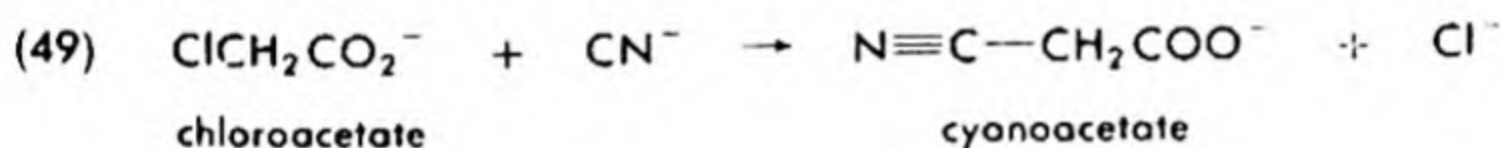


an imino ester salt to an amidine salt is illustrated in eq. (47). This is a solvolysis similar to ammonolysis of an ester (§17-3D). Direct addition of ammonia or amines to nitriles occurs with difficulty.

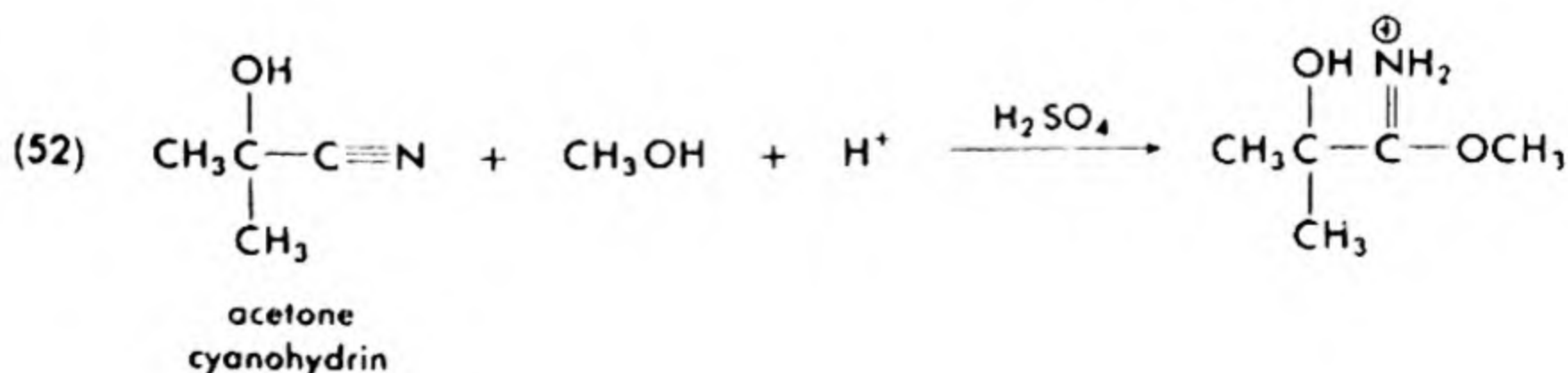
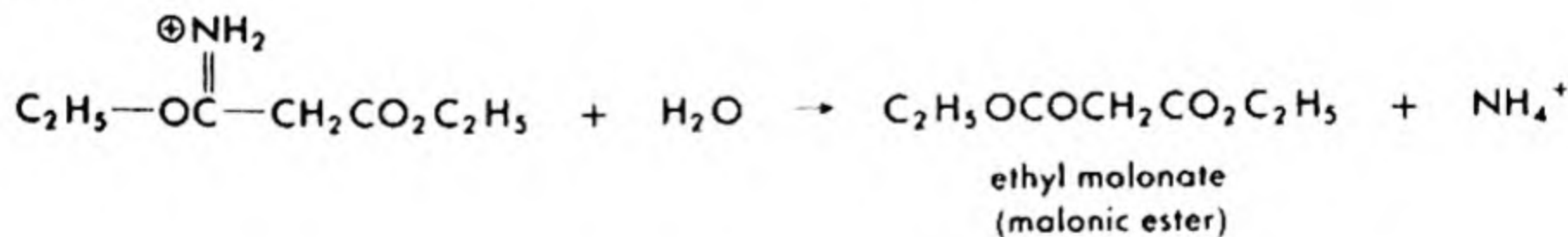
The imino group in imino esters is readily replaced by a keto group by treatment with water. This represents a very useful process for the formation of esters directly from nitriles (eq. 48). The reaction path, another

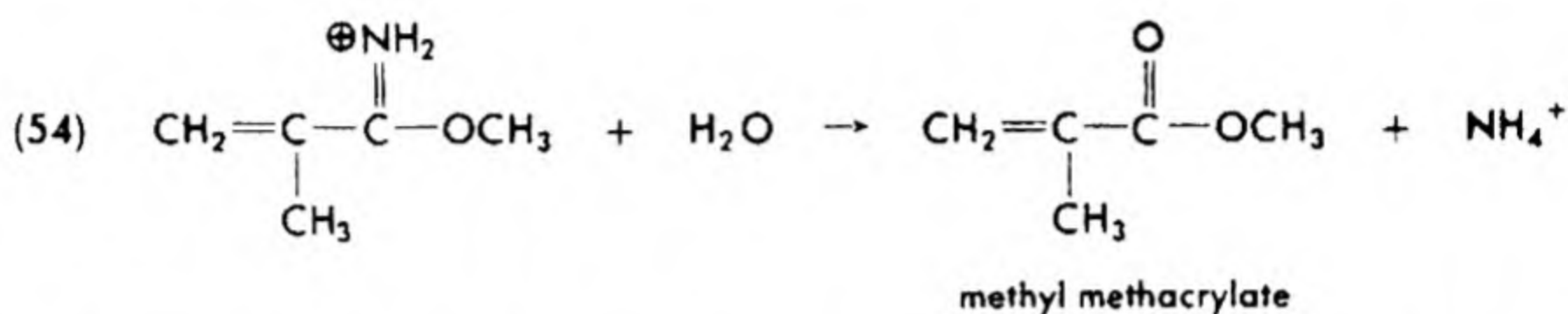
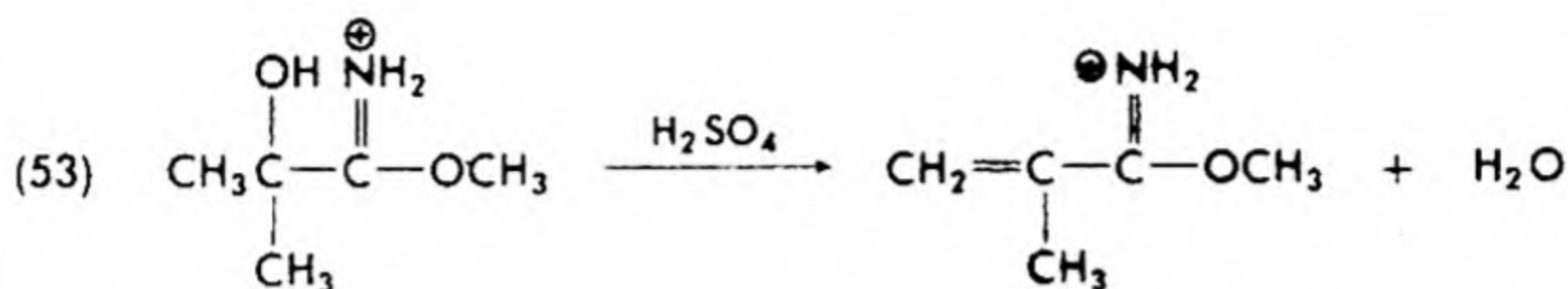


solvolysis example, undoubtedly involves addition of water to the functional carbon atom, proton migration, and loss of ammonia. This reaction is utilized industrially in the synthesis of malonic ester (see §21-6A) (eqs. 49-51) as well as in the synthesis of methyl methacrylate from acetone cyanohydrin (eqs. 52-54).

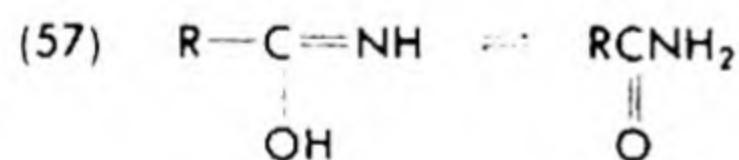
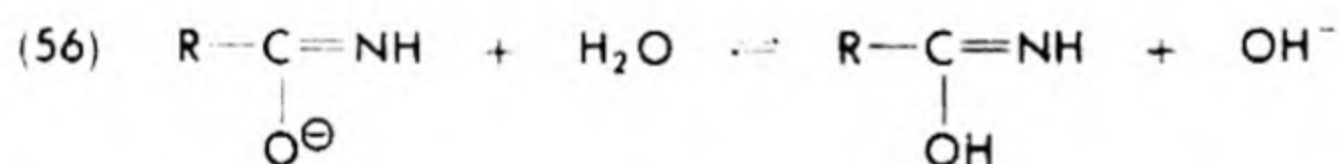


(51)





Esters of methacrylic acid (prepared with various alcohols by analogous processes) are important for the preparation of useful polymers (see §46-3E). Nitriles also undergo addition-displacement reactions with bases. Alkoxides form alkyl imidates, though the acid-catalyzed reaction is more convenient since it produces the more stable imino ester salts. Hydroxide ion forms the intermediate amide, which can proceed to the carboxylate salt without isolation. For reactions which follow eq. (57) see §17-3D.



SUPPLEMENTARY READINGS

- Gould, E. S., *Mechanism and Structure in Organic Chemistry*, Holt-Dryden, New York, 1959, pp. 539-544 and 549-552.
 Hine, J., *Physical Organic Chemistry*, 2nd Ed., McGraw-Hill, New York, 1962, pp. 249-257.
 Roger, R., and D. G. Neilson, "The Chemistry of Imidates," *Chem. Rev.*, **61**, 180-184, 191-195 (1961).

QUESTIONS AND PROBLEMS

1. Write equations for any reactions that go essentially to completion in the following mixtures of reagents. Use structural formulas for organic compounds. Indicate essential conditions.

- a. butanone and saturated sodium bisulfite solution b. *n*-butyraldehyde and water

- | | |
|---|--|
| c. diethyl ketone and hydrogen cyanide | g. crotonaldehyde and <i>n</i> -butyl alcohol |
| d. acetonitrile and limited amount of water | h. isobutyraldehyde and methanol |
| e. acetophenone and hydrochloric acid | i. 1,3-butanediol and formaldehyde |
| f. benzonitrile and isopropyl alcohol | j. 2,6-dimethyl-2,5-heptadien-4-one (phorone) and ethyl orthoformate |

2. Show how the following compounds can be prepared from acetaldehyde and inorganic reagents (including HCN and its salts).

- | | |
|----------------|-----------------------------------|
| a. lactic acid | d. α -chloropropionic acid |
| b. DL-alanine | e. 1-aminoethanesulfonic acid |
| c. ethylamine | |

3. Describe two ways an aldehyde can be isolated from a mixture of the aldehyde and higher ketones (other than methyl) by chemical means.

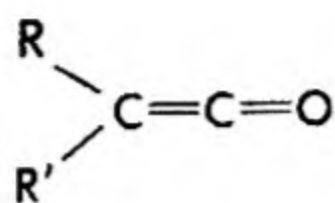
4. Describe a method by which a carbonyl compound can be isolated from a mixture of the carbonyl compound with alcohols, olefins, or other noncarbonyl compounds by chemical means.

5. Show the steps necessary to bring about the following transformations in good yield. Indicate reagents and conditions. Use structural formulas for organic compounds.

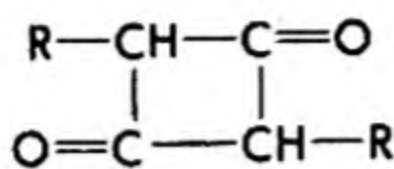
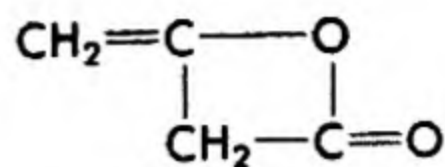
- | | |
|--|--|
| a. <i>n</i> -butyraldehyde to <i>n</i> -butyraldehyde sodium bisulfite and back to <i>n</i> -butyraldehyde again | f. <i>p</i> -hydroxyphenylacetaldehyde to tyrosine (2-amino-3-[4-hydroxyphenyl]propanoic acid) |
| b. ethanol to acetaldoxime | g. acetone to 2-hydroxy-2-methylpropanoic acid |
| c. propanol to 1,1-dipropoxypropane | h. benzyl cyanide and isopropyl alcohol to isopropyl phenylacetimidate |
| d. butane-2,3-dione to dimethylglyoxime | i. formaldehyde and methyl sulfate to methoxyacetonitrile |
| e. cyanamide and ethanol to guanidinium chloride | |

18-3 ADDITION TO CUMULATED UNSATURATED SYSTEMS

Isocyanates, $R-N=C=O$, isothiocyanates, $R-N=C=S$, and ketenes, $R_2C=C=O$, have in common a cumulated unsaturated system with a carbonyl group, or thiocarbonyl group, at the end of the molecule. Cumulated unsaturated systems are highly reactive, hence make good synthetic intermediates. However, because of their reactivity, they are often difficult to preserve. Ketenes, especially, are best prepared just before use. Some ketenes can be stored as their dimers, which decompose on strong heating to give the ketenes. It is of interest that ketene itself gives the β -lactone dimer, while substituted ketenes give cyclobutane-diones.

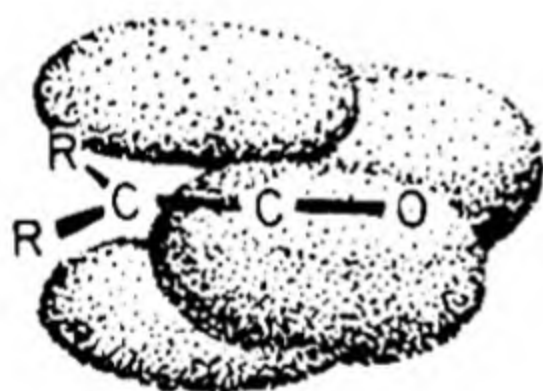
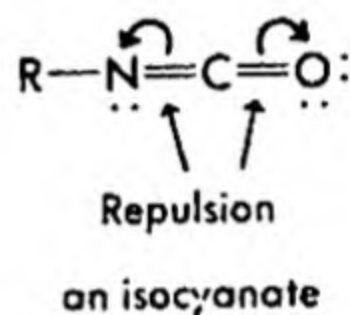
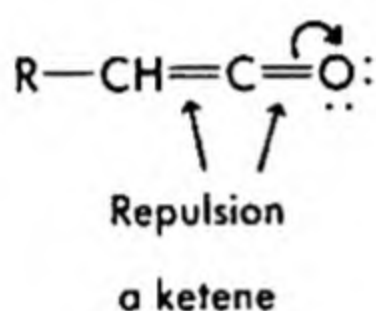


a ketene

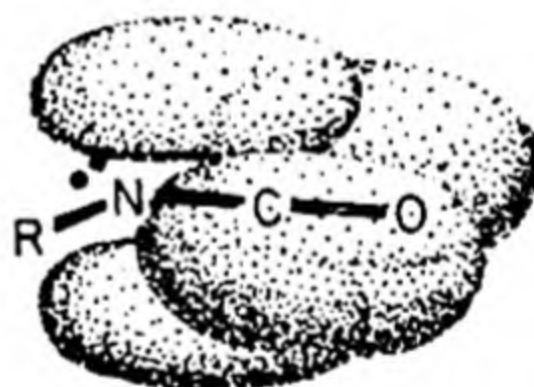
a cyclobutanedione
ketene dimera β -lactone
ketene dimer

A. Reactivity of the Cumulated System

Most of the substances that add to aldehydes and ketones also add to ketenes, isocyanates, and isothiocyanates, but with greater vigor. Whereas reactions of aldehydes and ketones are essentially reversible, few of those of ketenes, isocyanates, and isothiocyanates are, and then only under special, drastic conditions (see §18-3B). These differences are probably due to the instability of the cumulated double bonds, resulting from the repulsions of the nonoverlapping π -orbitals (below and Fig. 18.1), which lie at right angles to each other.



A



B

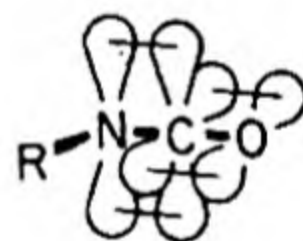
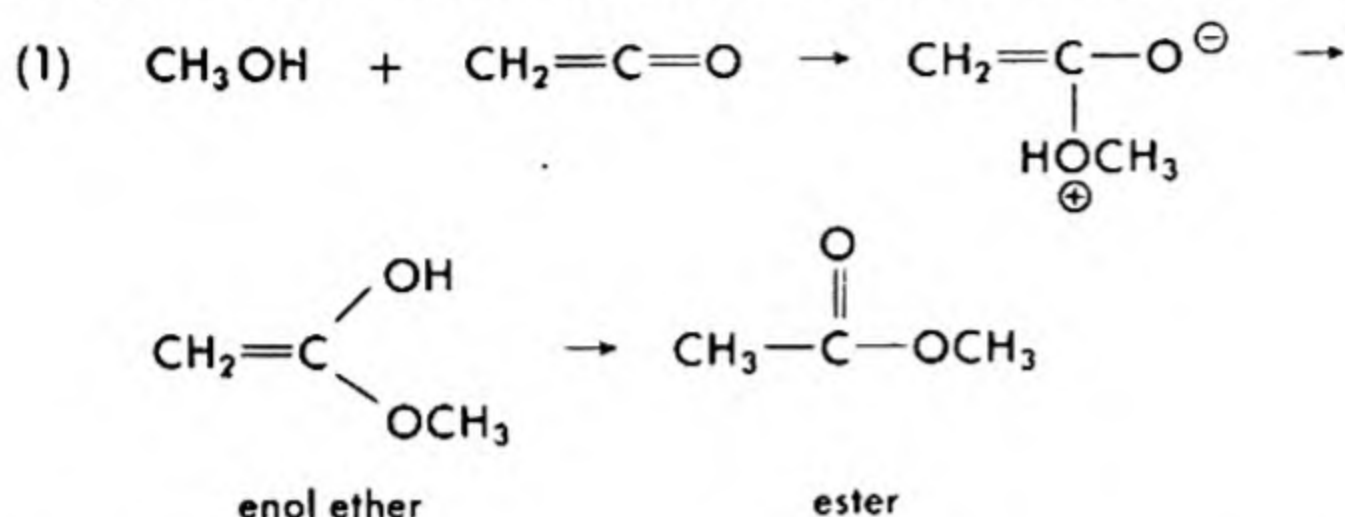


Fig. 18-1. Cumulated Systems: MO Clouds and Orbital Formulas. (A) Ketenes, (B) Isocyanates.

Ketenes are the most reactive of these compounds, isocyanates next, and isothiocyanates least reactive. Thus, ketenes react with water in the absence of catalyst, as do isocyanates, while isothiocyanates may in some cases be steam distilled. Alcohols react with ketenes and isocyanates, but again not with isothiocyanates. Ammonia and amines react readily with all three. Tertiary amines are often used as catalysts for the addition reaction.

Mechanisms for additions are similar to those for addition to carbonyl groups. Thus, in the addition to ketene of methanol, the reaction prob-

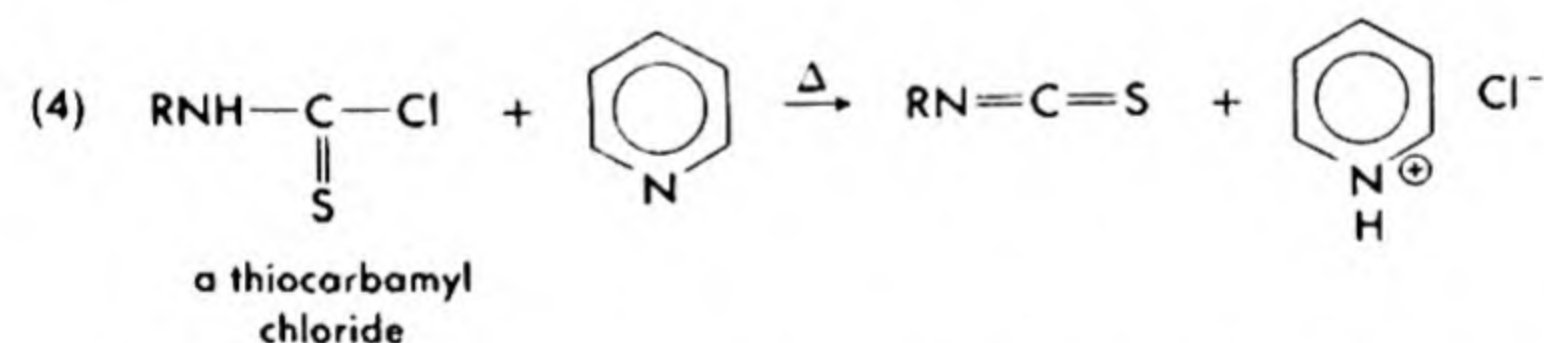
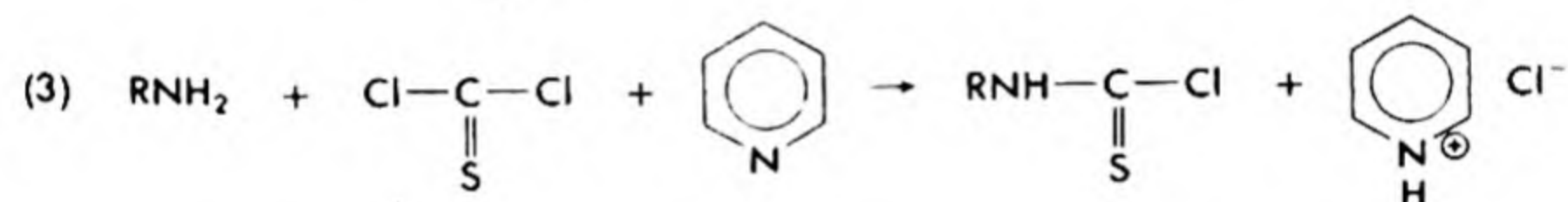
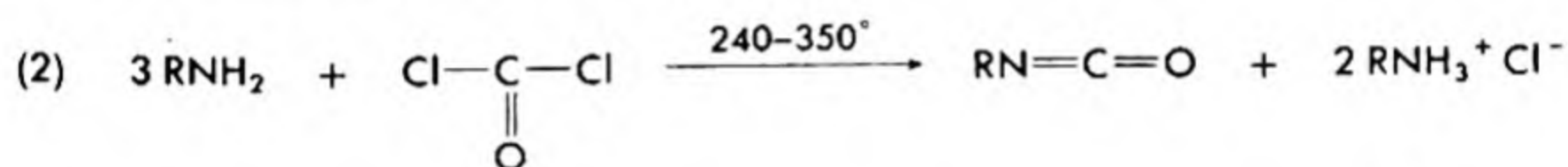
ably takes the course shown in eq. (1). The enol tautomer is probably the



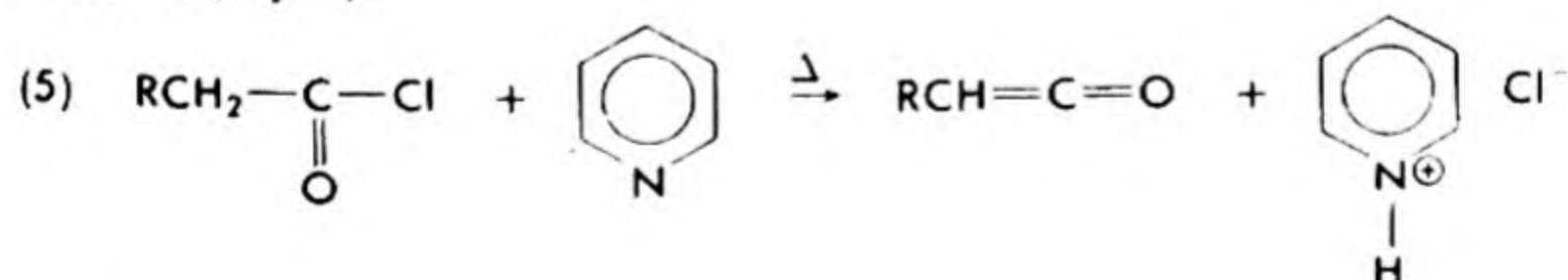
first product but rearranges immediately to the normal ester.

B. Preparation of Isocyanates and Ketenes

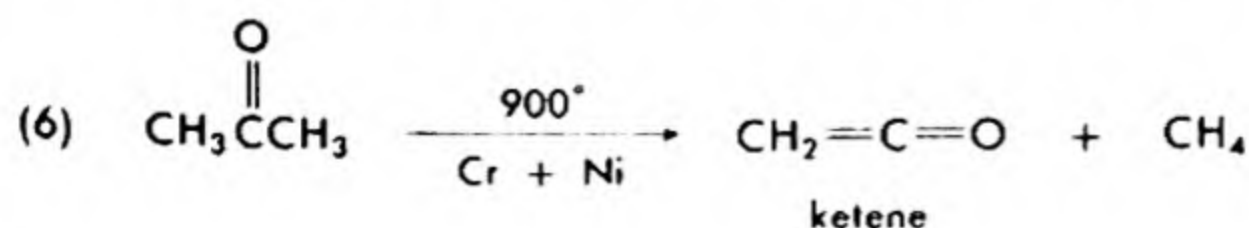
Isocyanates and isothiocyanates are prepared from amines and phosgene or thiophosgene under conditions more drastic than those commonly used in amide preparation (eqs. 2-4).



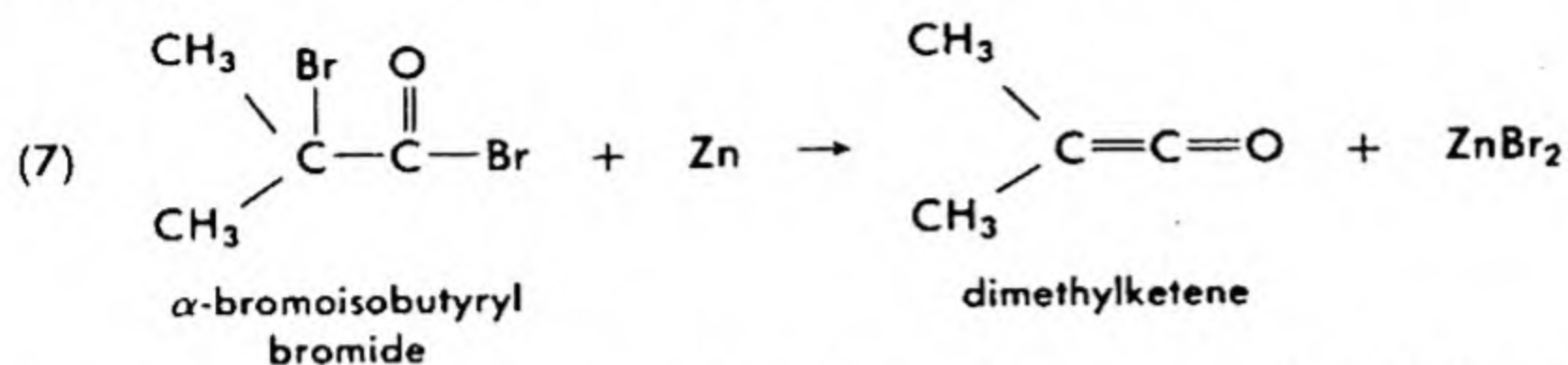
One method for the preparation of ketenes is similar to the dehydrochlorination of the thiocarbamyl chloride (eq. 4). An acyl halide is heated under reflux with pyridine, the more volatile ketene distilling as it is formed (eq. 5).



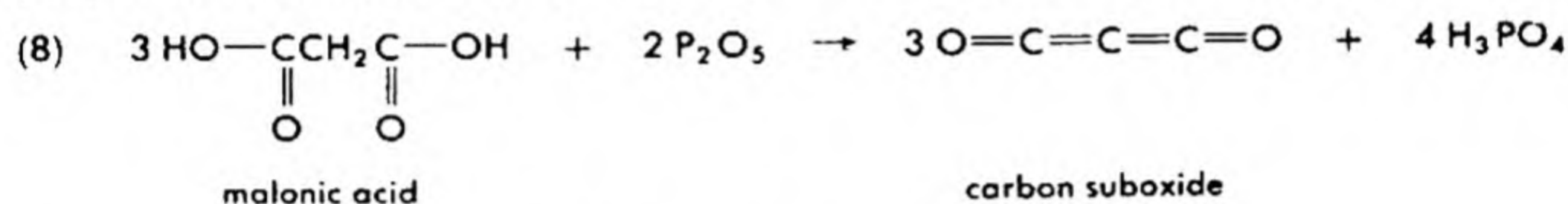
Unsubstituted ketene is usually prepared by pyrolysis of acetone (eq. 6) over a red-hot chromel wire. The optimum yield of ketene is about 90%.



Ketoketenes are generally prepared from α -bromoacyl bromides and zinc (eq. 7). An interesting ketene-like compound, carbon suboxide, is



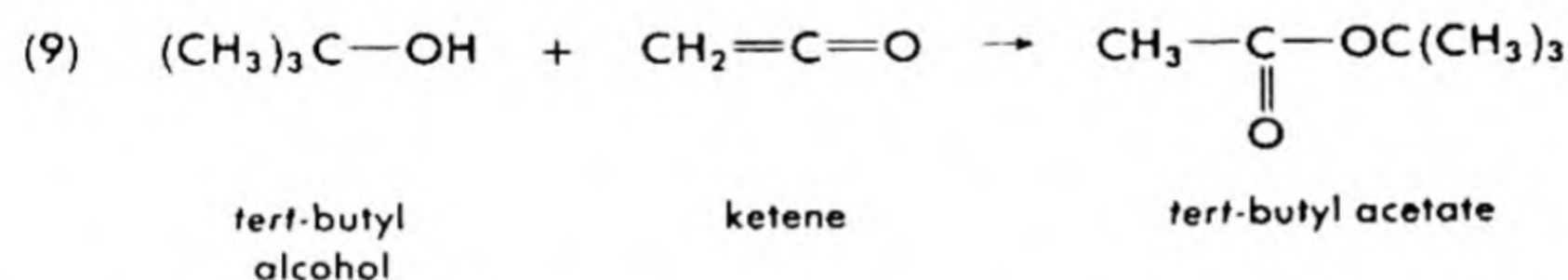
prepared when malonic acid is dehydrated (eq. 8). This compound is one



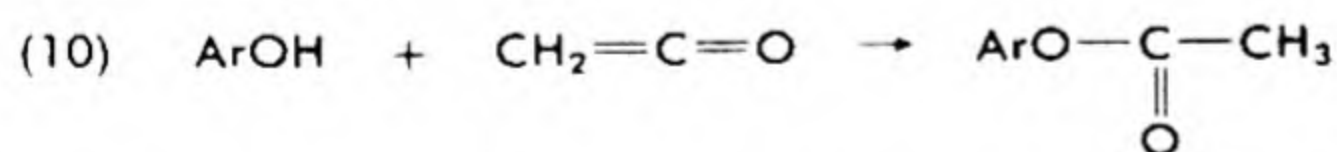
of several unusual organic "oxides" of carbon.

C. Typical Additions

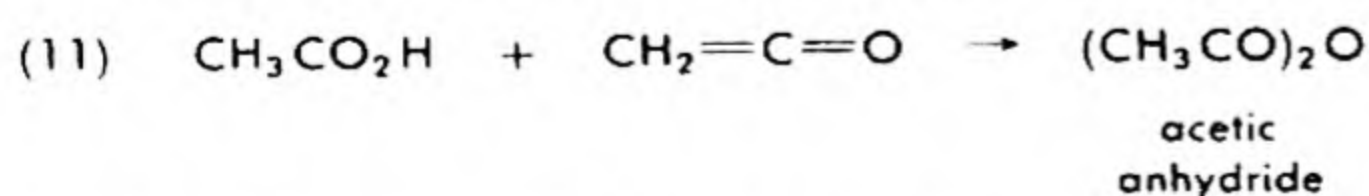
Ketene is most useful for preparing derivatives of acetic acid which can be prepared only with difficulty in other ways. For example, ketene reacts with tertiary alcohols to form acetates which are prepared only in poor yield by the usual methods of esterification.



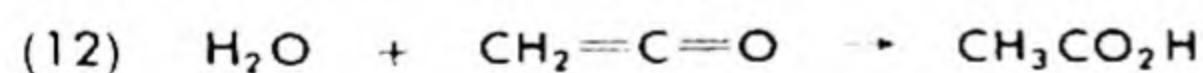
Phenols are also sometimes difficult to esterify. High yields of esters are obtainable by use of ketene.



The reaction of ketene with acetic acid leads to acetic anhydride.

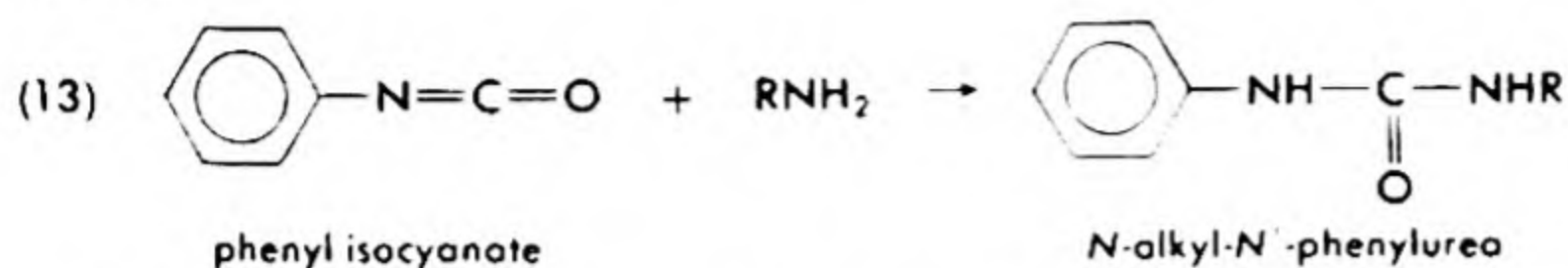


Needless to say, reagents for use with ketene must be scrupulously dried, as water reacts to give acetic acid (eq. 12) which then reacts with more ketene to give acetic anhydride (eq. 11). Other compounds which add to

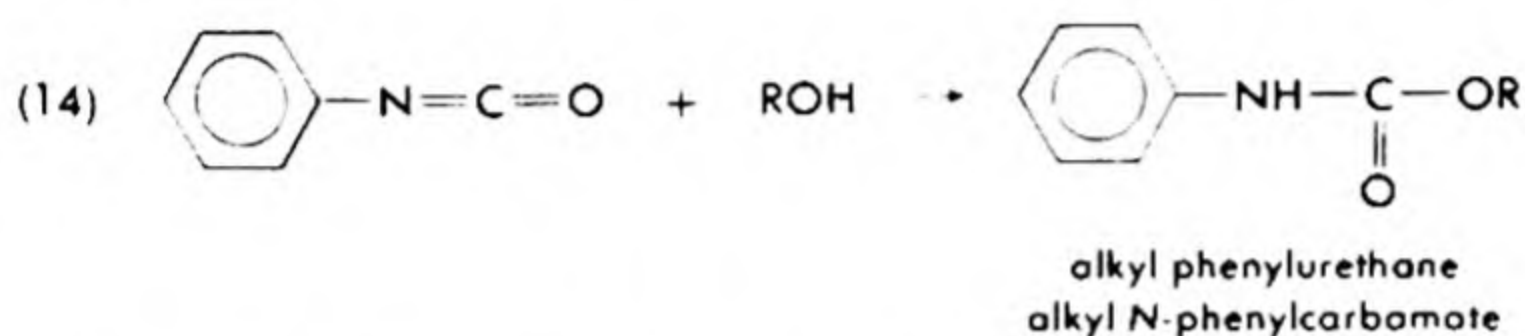


ketene to give useful acetic acid derivatives are hydrogen halides and hydrogen sulfide. Acetyl halides and thioacetic acid are the products.

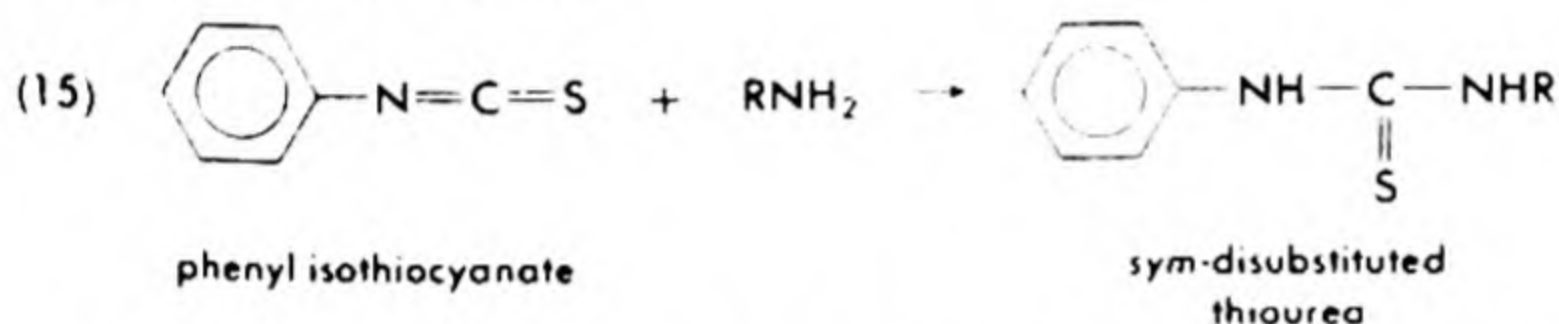
Phenyl isocyanate is used as a reagent to form derivatives for the characterization of either amines or alcohols. Amines form substituted ureas.



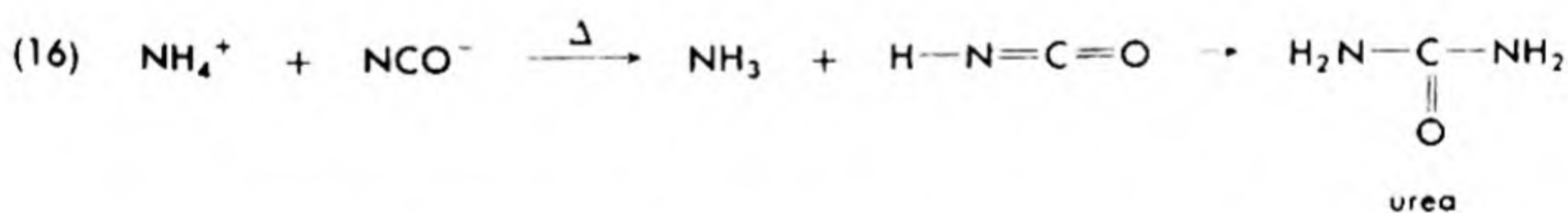
The products from alcohols are *N*-phenylcarbamates or urethanes. Polyurethanes formed by reactions of diisocyanates and polyols form an important class of high polymers. The products may be resins or rubbers (see §46-5E).



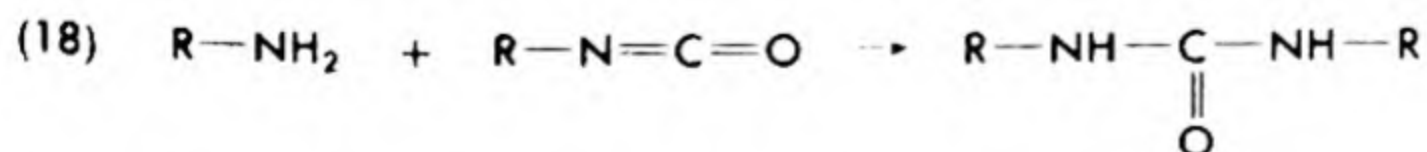
Phenyl isothiocyanate is also used as a reagent to identify amines by formation of thioureas.



Wöhler's classical synthesis of urea from supposedly inorganic compounds can be considered to be an addition to an isocyanate.



Isocyanates also react with moisture to give carbamic acids which decarboxylate immediately to amines, which in turn react with more of the reagent to give symmetrically substituted ureas. Since diphenylurea, di- α -naphthylurea, and the like formed in these reactions are generally much

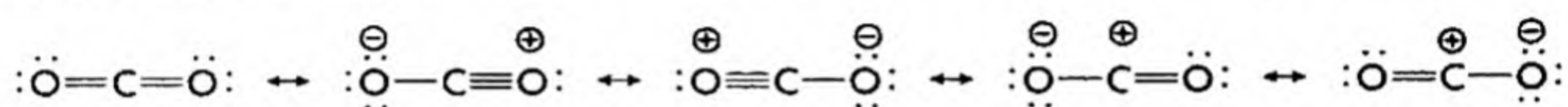


less soluble in crystallization solvents than the urea derivatives desired, they give considerable trouble in the purification of the desired

products. For this reason, amines from which ureas are to be prepared must be scrupulously freed from moisture. The same applies to alcohols before they are converted into alkyl *N*-arylcarbamates. As isothiocyanates do not react with water, the preparation of dialkylthioureas is often preferred for making derivatives of amines.

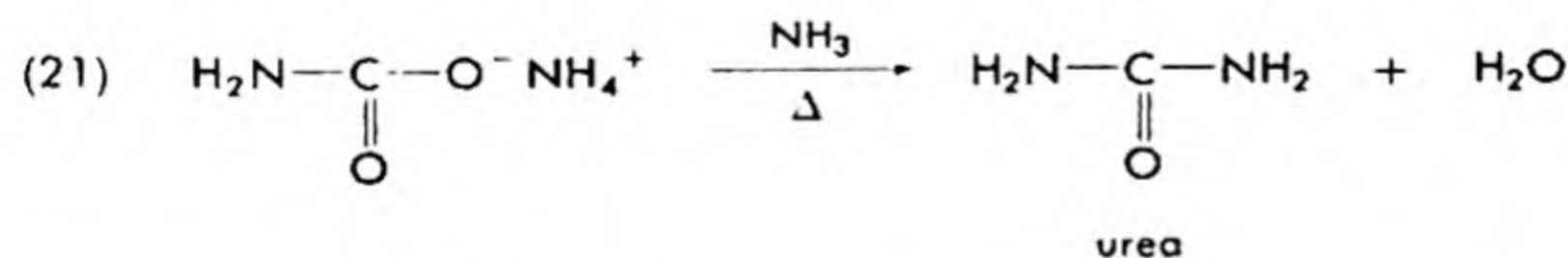
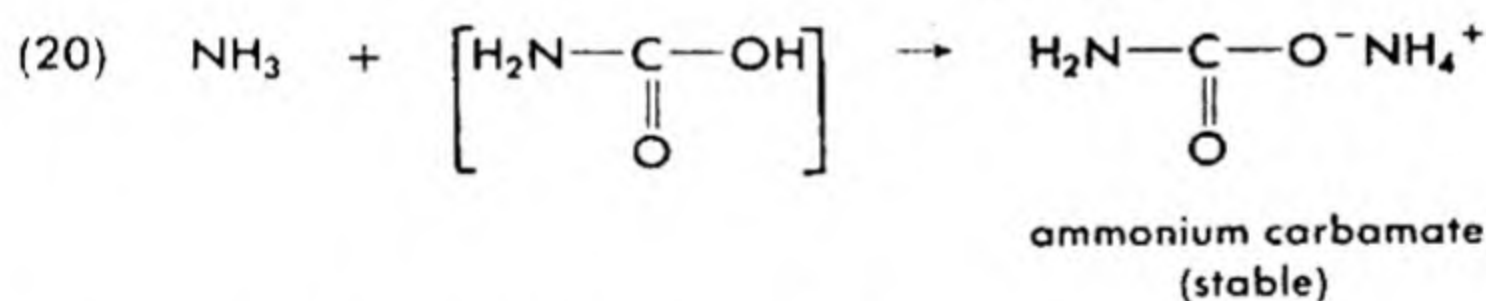
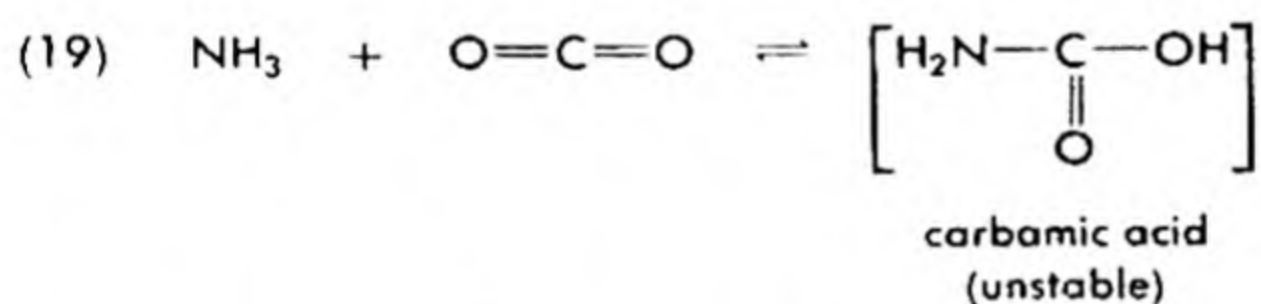
D. Additions to Carbon Dioxide and Carbon Disulfide

Carbon dioxide and carbon disulfide are cumulated compounds analogous to isocyanates and isothiocyanates, respectively. However, carbon dioxide is much less reactive than the isocyanates, possibly due to resonance stabilization. Similar factors contribute no unusual stability to

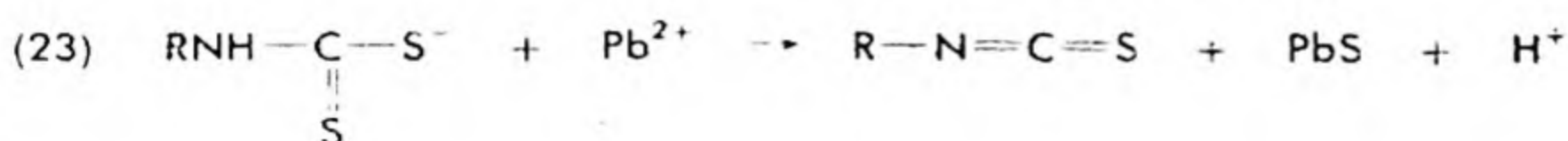
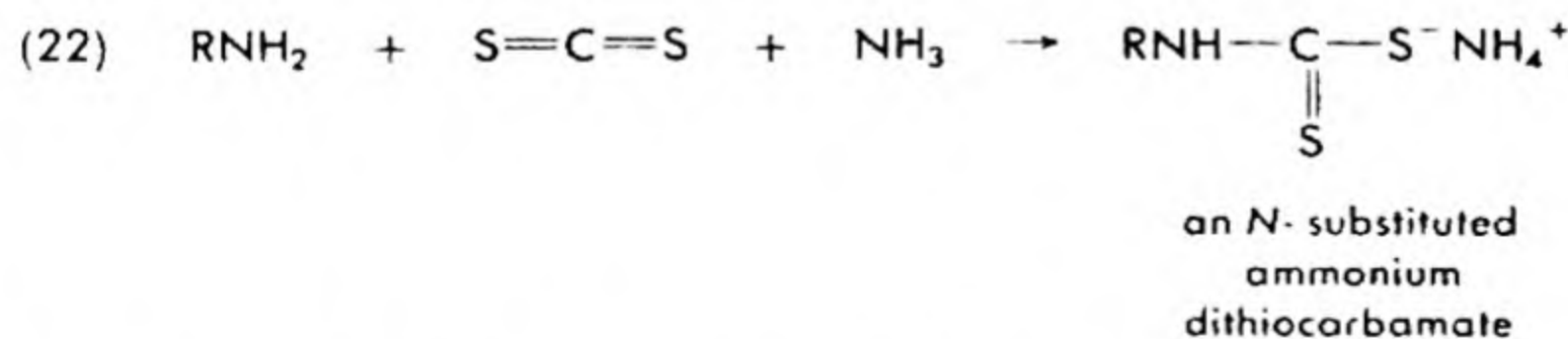


carbon disulfide, as the sulfur atom forms multiple bonds with difficulty.

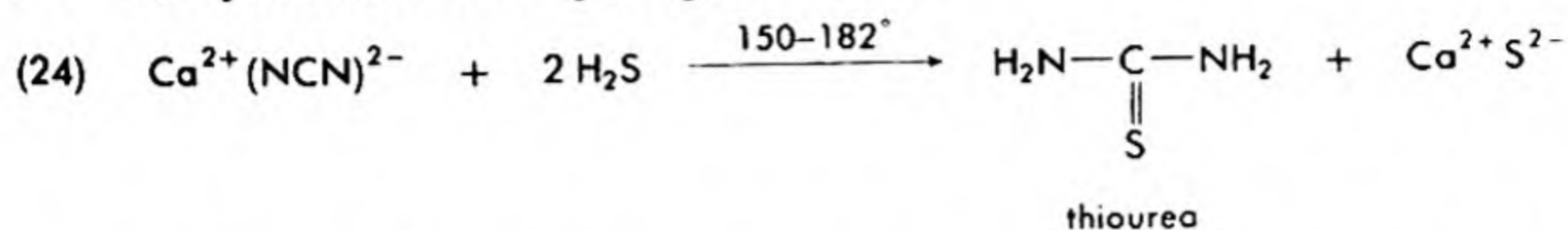
Carbon dioxide and carbon disulfide add ammonia and amines to form carbamates and dithiocarbamates, respectively. Ammonium carbamate is converted to urea industrially by heating (eqs. 19–21). Ammonium dithio-



carbamates (eq. 22) are intermediates in one method for the preparation of isothiocyanates (eq. 23).

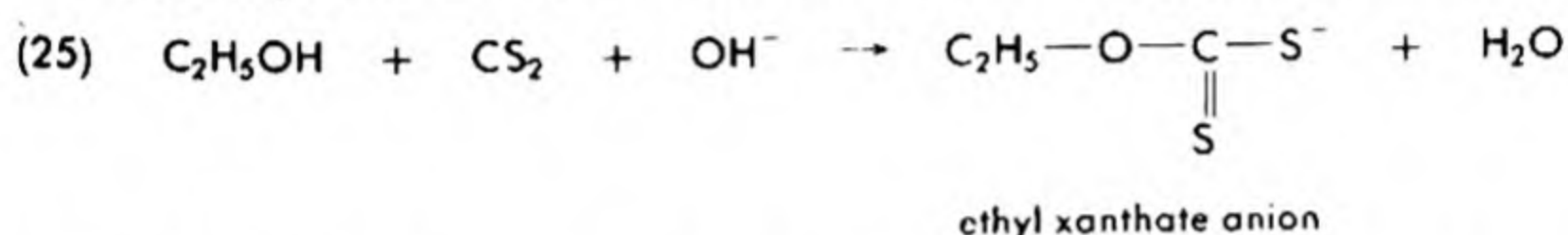


Thiourea is not readily prepared from ammonium dithiocarbamate by a process analogous to eq. (21), but is available from the reaction of calcium cyanamide and hydrogen sulfide.

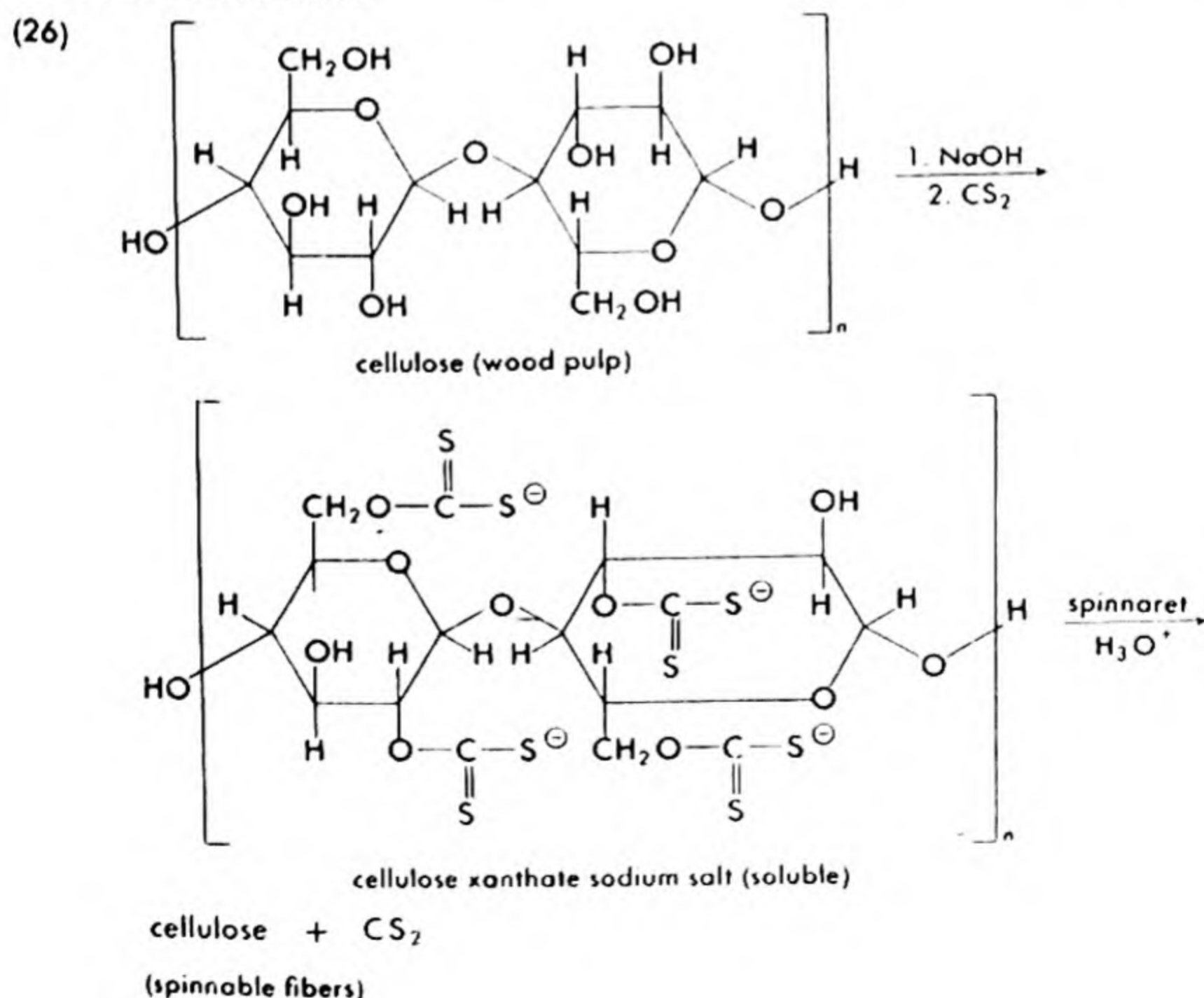


Metallic *N*-alkyldithiocarbamates, prepared from the ammonium salts, are useful commercially as pesticides for fungi and certain weeds.

Reactions of carbon disulfide with base are analogous to those of carbon dioxide. One commercially important reaction of carbon disulfide is that with alcohols in the presence of base to form xanthates (eq. 25). These are decomposed in acid solution to the original alcohol and carbon



disulfide. This feature is useful for the formation of viscose rayon. Cellulose is dissolved by xanthate formation, then redeposited in fine filaments by running the viscose solution (the xanthate) through "spinnerets," dies with tiny orifices, into acid solution. The carbon disulfide can be recovered and reused.



SUPPLEMENTARY READING

Hanferd, W. E., and J. C. Sauer, "Preparation of Ketenes and Ketene Dimers," *Org. Reactions*, 3, 108-140 (1946).

QUESTIONS AND PROBLEMS

1. How do ketenes differ in reactivity from aldehydes and ketones? Why?
2. What do you predict to be the relative reactivities of amides and isocyanates? Why?

3. Write equations for any reactions that go essentially to completion in the following mixtures of reagents. Use structural formulas for organic compounds.

- | | |
|---|---|
| a. phenyl isocyanate + excess dilute sodium hydroxide | e. <i>n</i> -amyl isothiocyanate + <i>n</i> -propyl mercaptan |
| b. ketene + diethyl ether | f. cyclopentyl isocyanate + dimethylamine |
| c. methylketene + hydrogen sulfide | g. carbon disulfide and aniline |
| d. dimethylketene + methyl iodide | |

4. Show how the following compounds can be prepared in good yield from the indicated starting materials. Use structural formulas for organic compounds. Indicate inorganic reagents and conditions.

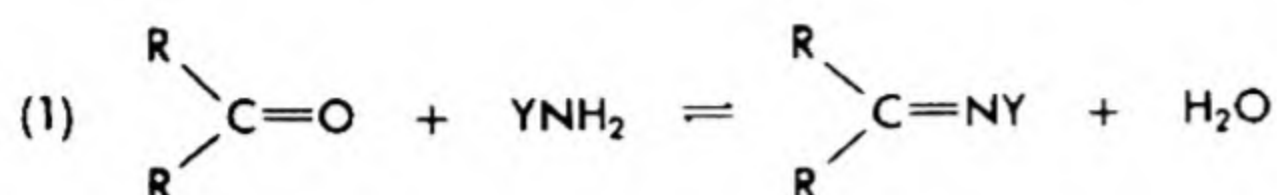
- | | |
|---|---|
| a. diphenylurea from phenyl isocyanate | f. phenylketene from phenylacetic acid |
| b. isobutylamine from isobutyl isocyanate | g. acetic anhydride from acetone |
| c. ethyl urethane from ethyl isocyanate | h. α -naphthyl isocyanate from α -naphthylamine |
| d. thioacetic acid from ketene | i. thiourea from potassium thiocyanate |
| e. <i>n</i> -butyramide from ethylketene | j. <i>n</i> -butyl acetate from ketene |

18-4 CARBONYL OXYGEN DISPLACEMENTS

The reactions considered in this section are of the type exemplified by the formation of oximes, phenylhydrazones, semicarbazones, and other derivatives of aldehydes or ketones.

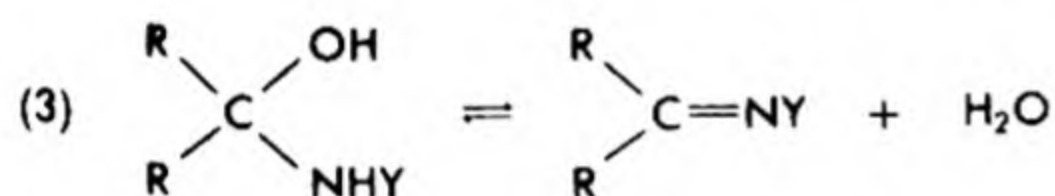
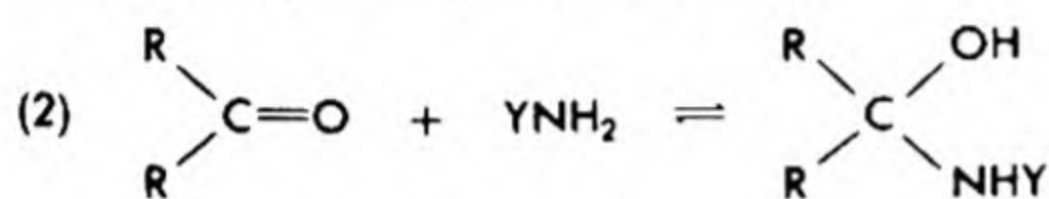
A. Displacement Agents

Any electron-donating molecule or ion which establishes a bond with the carbonyl carbon atom either more stable than or of approximately equal stability to the carbon-oxygen bond, such as the carbon-nitrogen bond, reacts. For the reaction to be a replacement, not an addition, the other requirement is that the added group have a hydrogen atom to lose from the addition complex. Compounds which characteristically undergo carbonyl replacements are the substituted ammonias: amines, hydroxylamines, hydrazine, phenylhydrazine, semicarbazide, etc. The overall reaction is given in eq. (1).



B. Specific Mechanisms for the Reactions

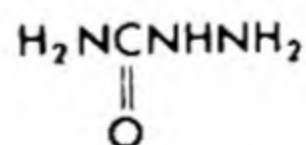
Most of these displacement reactions are subject to acid catalysis, but high concentrations of strong acids cannot be used, as they form salts with the amine component and remove them from the reaction. Salts of the amine component with weak acids are generally utilized. The reaction involves addition of the amino compound to the carbonyl group (eq. 2) followed by loss of water (eq. 3).



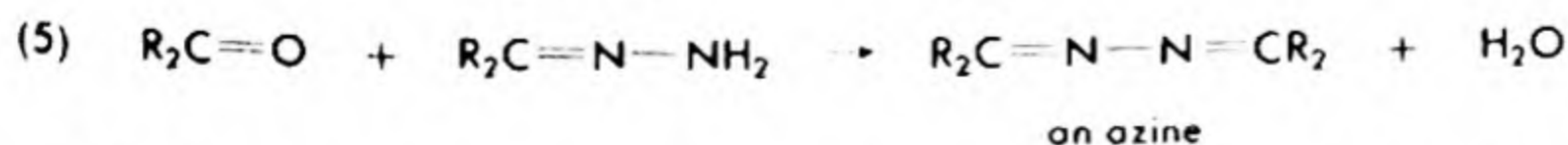
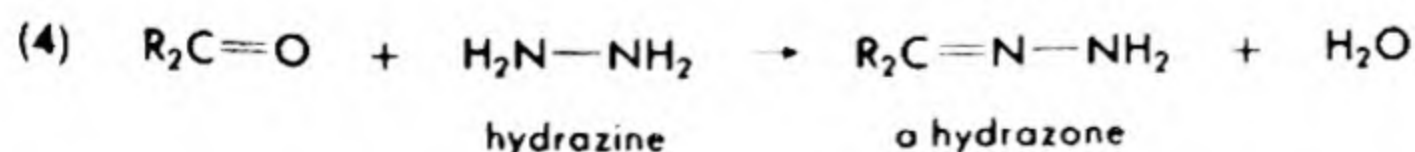
Even in aqueous media, the reactions proceed to the right, partly because many of the derivatives are insoluble in water. The success of the reaction is generally measured by the ease with which the products are induced to crystallize. Addition of significant quantities of a strong acid in aqueous solution causes the hydrolysis of the derivatives and shifts the equilibrium (eq. 1) to the left by forming salts of the amino compound.

C. Typical Reactions

The reactions of aldehydes and ketones with hydroxylamine, phenylhydrazine, 2,4-dinitrophenylhydrazine, and semicarbazide are so general that these reactions are used as diagnostic for the carbonyl group as well as for the preparation of derivatives to characterize individual compounds. Hydrazine reacts with either 1 or 2 moles of carbonyl compound (eqs. 4 and 5) to give hydrazones or azines.

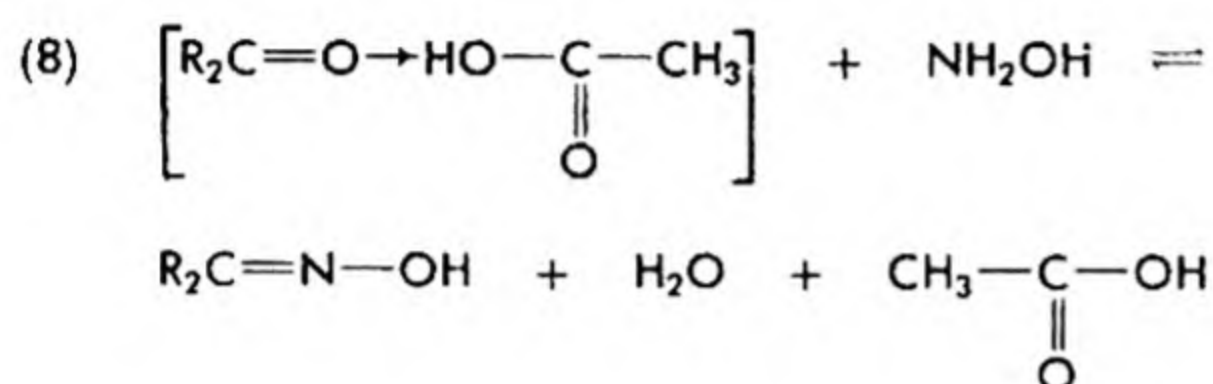
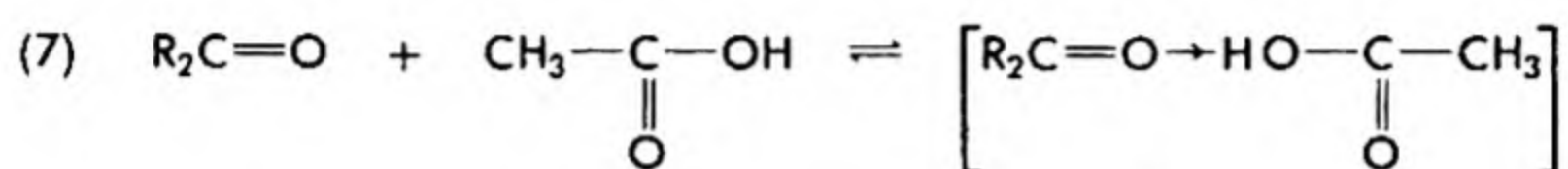
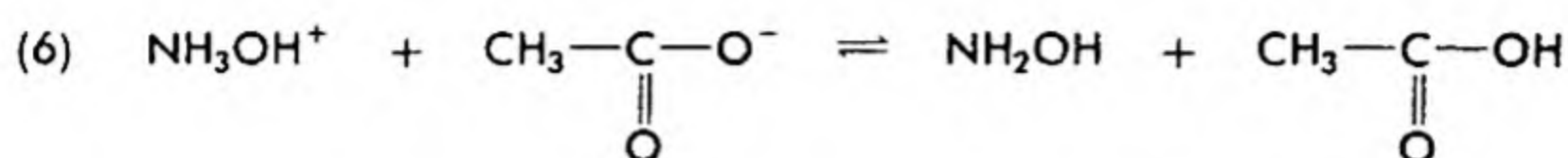


semicarbazide

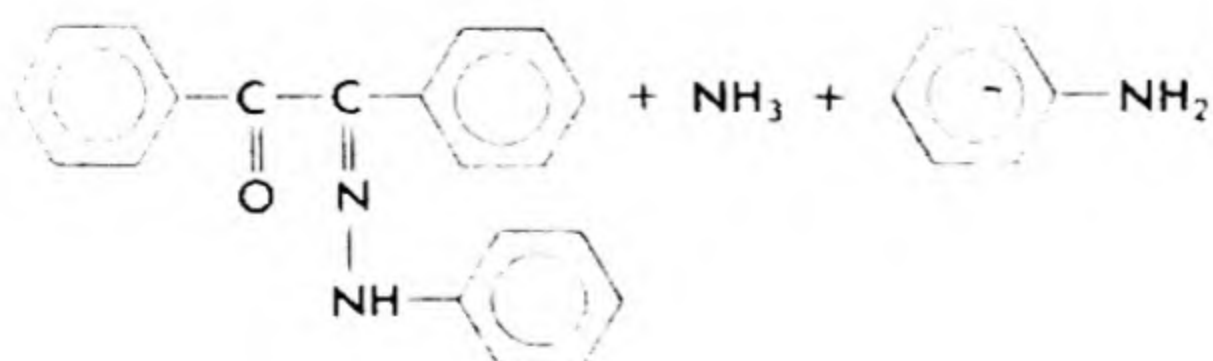
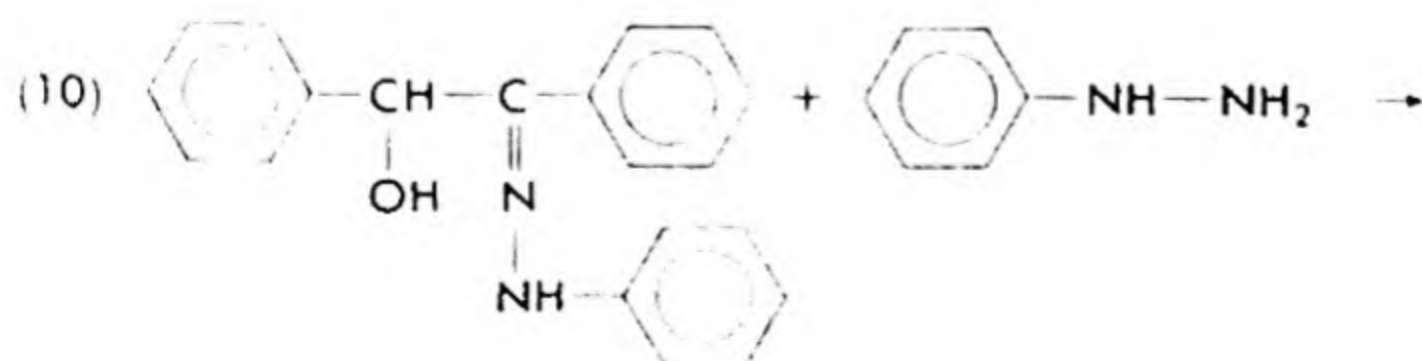
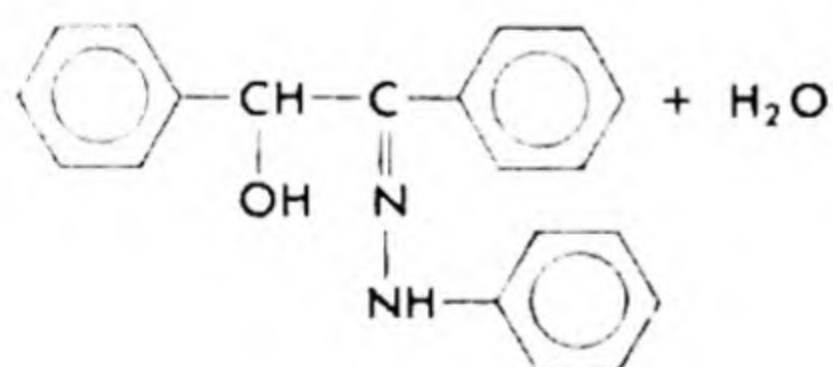
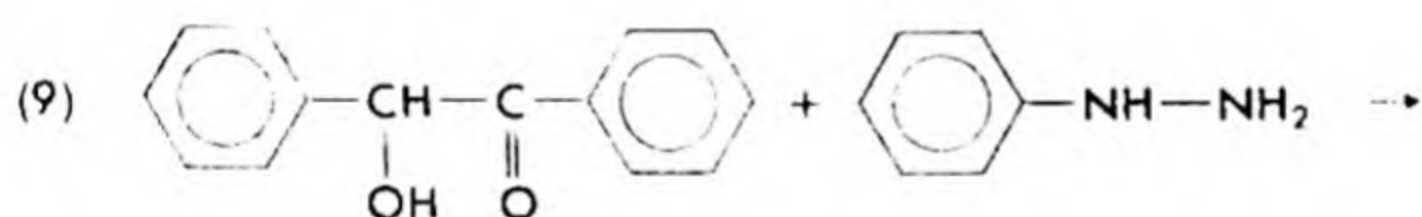


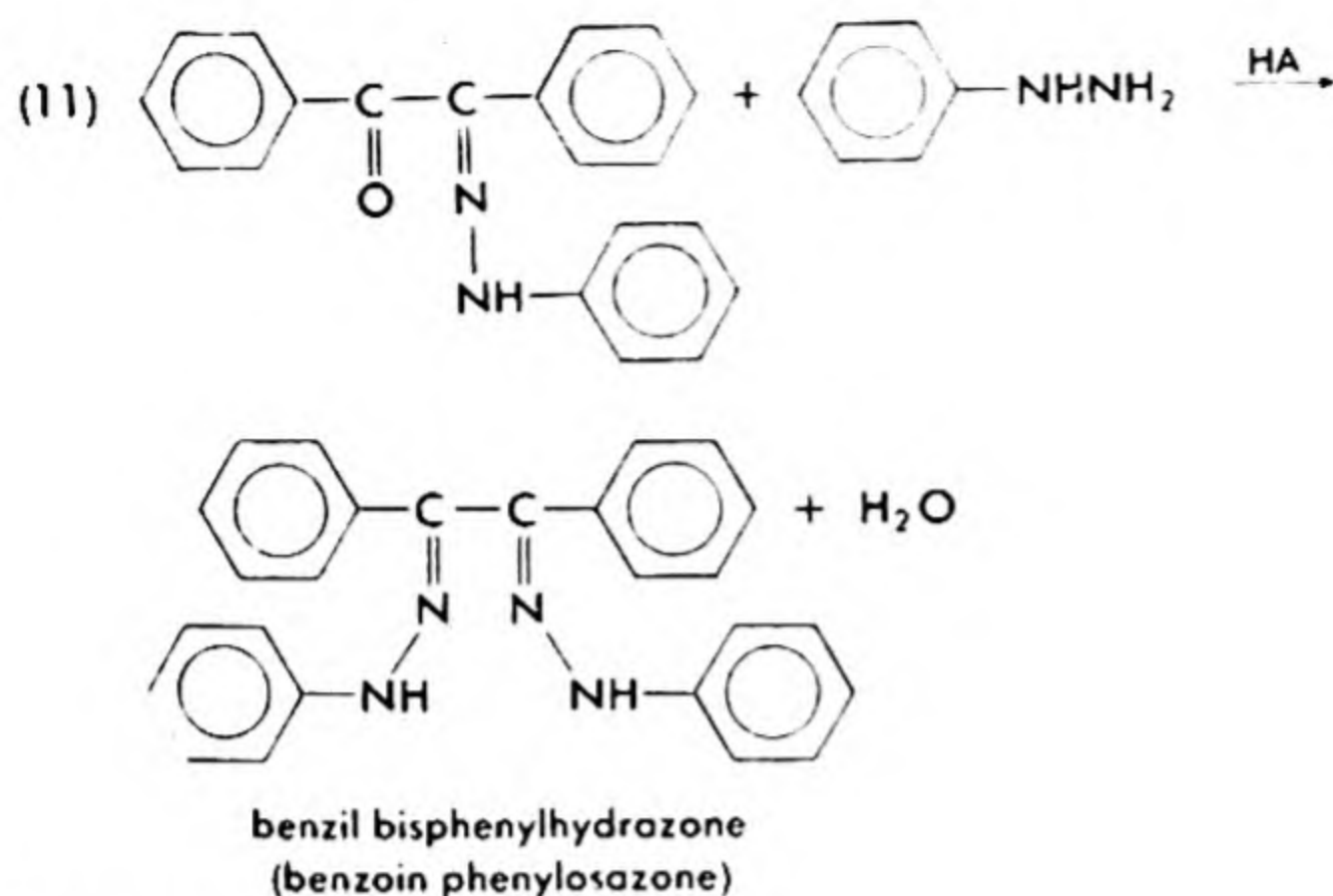
The bases required for the formation of such derivatives are rather easily oxidized by air. Hence, they are commonly stored as their salts

(chlorides or sulfates) and released for use by the addition of sodium acetate. The weak acid, acetic acid, catalyzes the reaction.



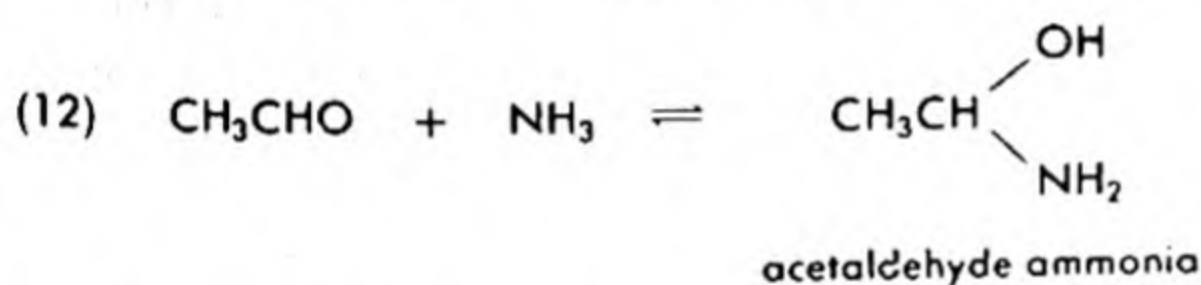
α -Hydroxyaldehydes and α -hydroxyketones react further with phenylhydrazines to form dihydrazones called *osazones*. The hydroxy group of the initial phenylhydrazone is oxidized, then reacts with a third mole of phenylhydrazine.



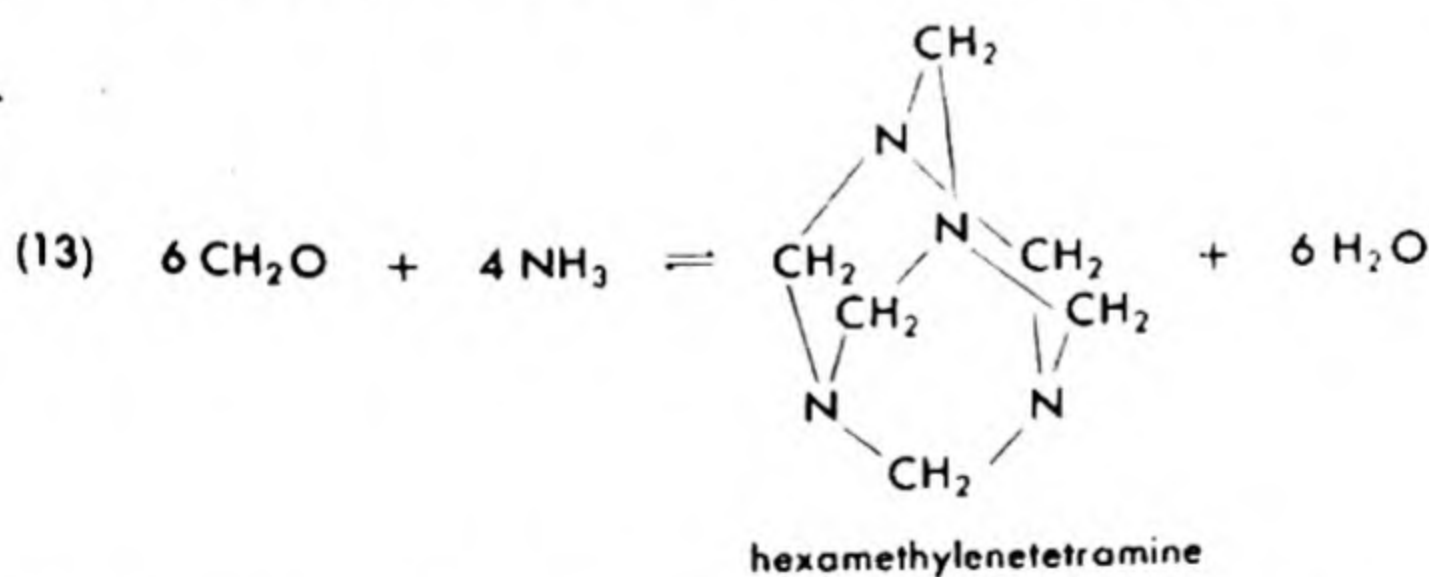


D. Aldehyde Ammonias

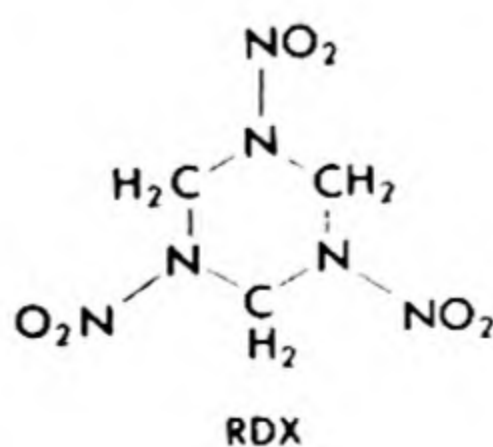
Certain aldehydes add ammonia to give simple addition compounds which can be isolated. An example is given with acetaldehyde (eq. 12).



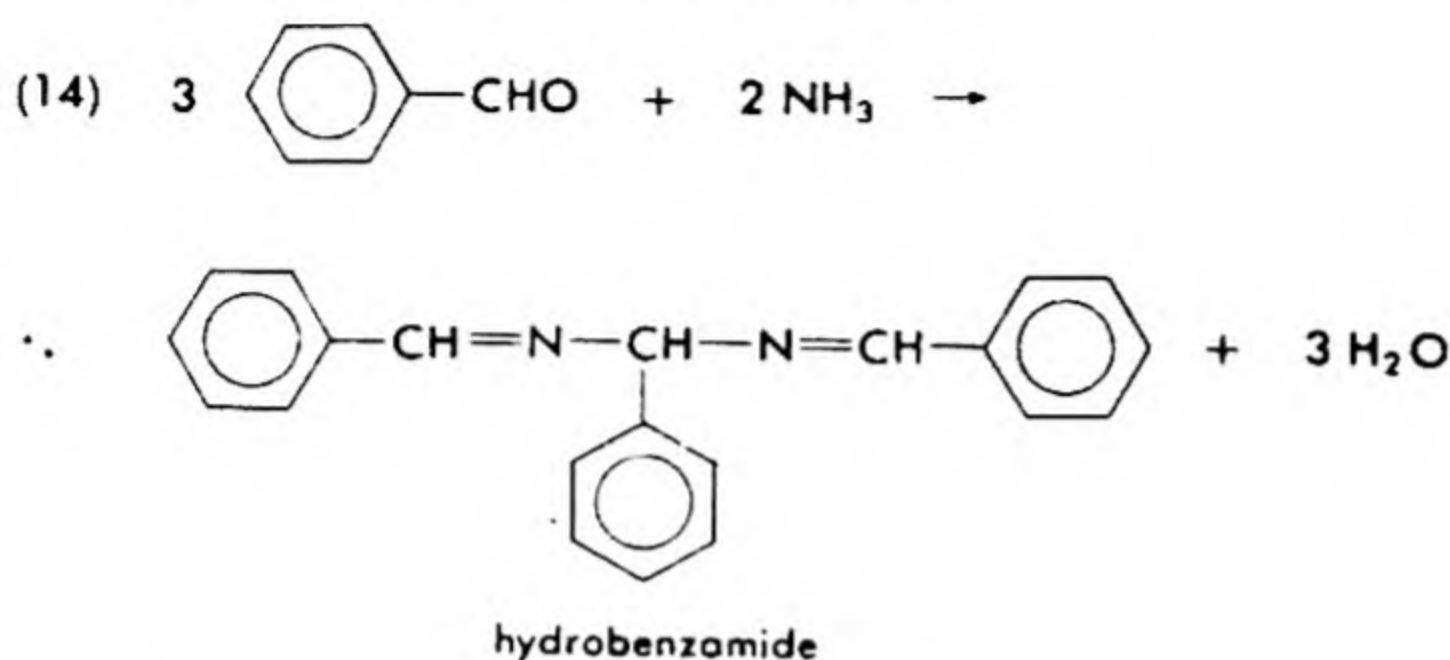
With formaldehyde, the aldehyde ammonia product condenses further to give hexamethylenetetramine or urotropine (eq. 13).



This compound is used as a bladder disinfectant and as an intermediate in the synthesis of the nitramine high explosive, RDX, by treatment with nitric acid.



Benzaldehyde undergoes a combination of additions and displacements leading to hydrobenzamide (eq. 14).



E. Schiff Bases

Only aldehydes form Schiff bases with simple primary amines, and then only if one or both reagents are aromatic. The presence of the aromatic ring in conjugation with the double bond in the product is apparently necessary to provide stability. The production of ethylideneaniline (eq. 15) and benzalaniline (eq. 16) are examples of the reaction. These products are called aldimines in systematic nomenclature.



QUESTIONS AND PROBLEMS

1. Write the overall equation for the preparation of benzaldoxime from benzaldehyde. What favors the going to completion of this reaction? How can the reaction be driven backward, thus hydrolyzing the oxime?

2. Write equations for the reactions that occur when the following compounds are mixed. Use structural formulas for organic compounds.

- | | |
|--|---|
| a. acetaldehyde + hydroxylamine | f. anisaldehyde + hydrazine |
| b. benzaldehyde + aniline | hydrate, aldehyde in excess |
| c. acetone + phenylhydrazine | g. 3-hydroxy-2-butanone + 2,4- |
| d. benzophenone + semicarbazide | dinitrophenylhydrazine |
| e. acetophenone + excess hydrazine hydrate | h. biacetyl + <i>o</i> -phenylenediamine |
| | i. benzil (1,2-diphenylethane-1,2-dione) and ethylene diamine |

3. Show how the compounds below can be prepared in respectable yields from the suggested starting materials. Use structural formulas for organic compounds. Indicate the reagents used and essential conditions.

- | | |
|---|--|
| a. benzylhydrazine hydrochloride
from benzaldehyde | c. acetone semicarbazone from
acetic acid and semicarbazide |
| b. phenylbenzylamine from aniline
and benzaldehyde | |

19

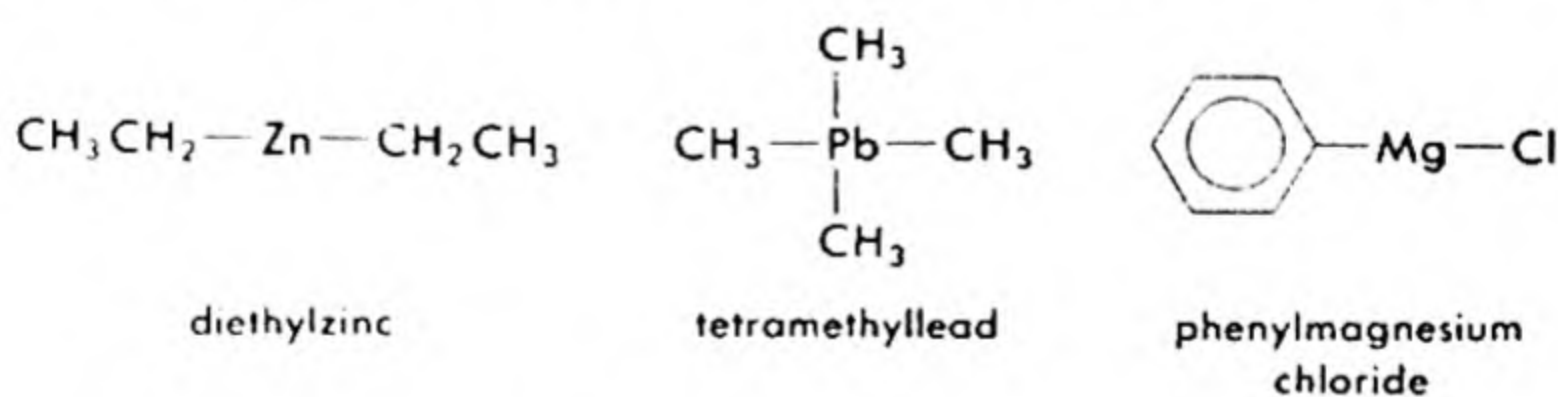
Organometallic Compounds and Organometalloids

19.1 NOMENCLATURE

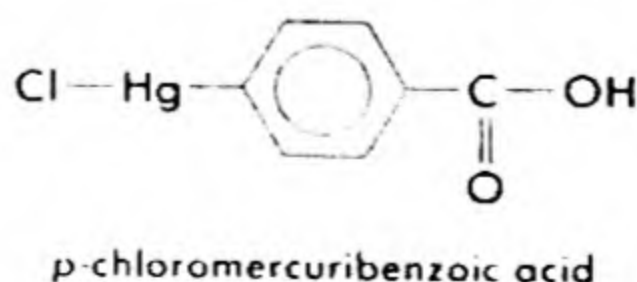
Organometallic compounds are substances in which a metal is chemically bound to carbon by a linkage which may be either ionic or covalent. In general, the more active the metal, the more reactive the organometallic compound derived from it, since the more active metals are more inclined to be cationic, whereas carbon strongly prefers covalence.

Organometalloids are alkyl or aryl derivatives of silicon, boron, and other elements which are not true metals, but which form organic derivatives which bear certain formal resemblances to organometallic compounds.

Both IUPAC nomenclature and common practice designate organometallic compounds by their component radicals followed by their metals, as diethylzinc, tetramethyllead, and phenylmagnesium chloride.



Prefixes are necessary in complex compounds having groups preferentially named as suffixes, as 4-chloromercuribenzenecarboxylic acid (IUPAC) or *p*-chloromercuribenzoic acid (common). Usually the metal prefix terminates in the syllable *-o*, as *sodio-*, *calcio-*, *magnesio-*. However, metals which have more than one valence use this syllable to designate



the lower valence and the syllable *-i* to indicate the higher valence. The prefix *mercuri-* in the preceding example indicates that the mercury is divalent. Similarly, *ferri* and *ferro* designate trivalent iron and divalent iron, respectively.

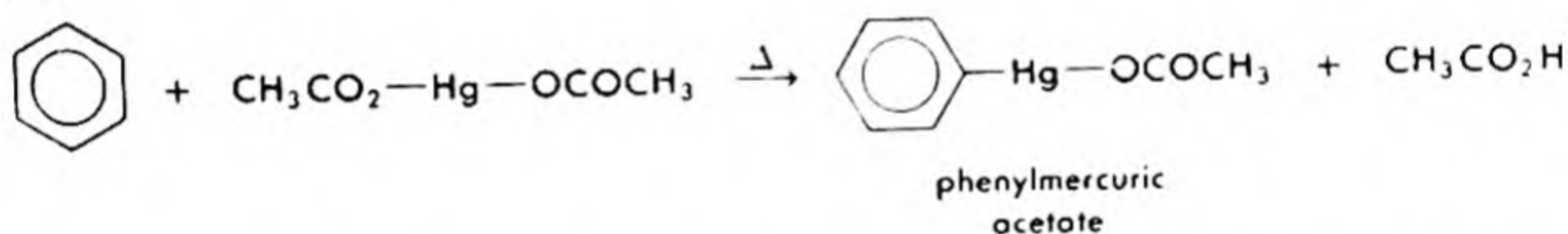
19-2 PREPARATION

Several general methods for preparing organometallic compounds, some of which are more suitable for one type, some for another, depending on the activity of the metal and the nature of the organic radical, are considered below.

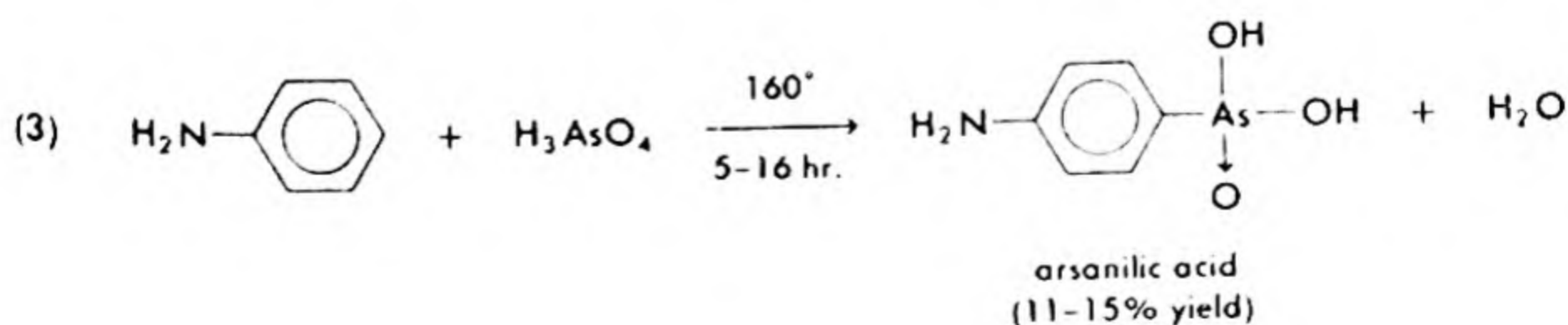
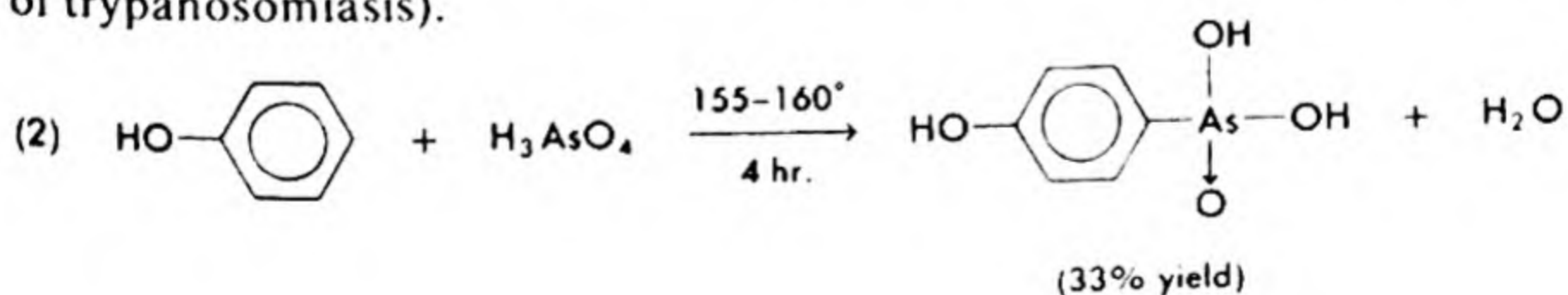
A. Direct Substitution: Metallation

Many organometallic compounds of relatively inactive metals can be prepared by electrophilic substitution by an electrophilic metal salt on an aromatic compound. For example, phenylmercuric acetate is manufactured in excellent yield by the action of mercuric acetate on benzene in glacial acetic acid. The product is a very useful fungicide, disinfectant, and spermicide.

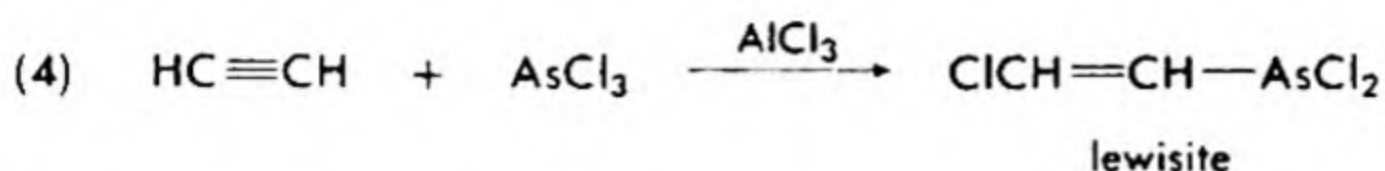
(1)



Less electrophilic arsenic in arsenic acid similarly attacks the very reactive aromatic substrates, aniline and phenol, but not less nucleophilic compounds. Even with activated aromatic compounds such as aniline and phenol, the substitution is very slow and gives low yields. Arsanilic acid and related compounds have been used to treat sleeping sickness (a type of trypanosomiasis).

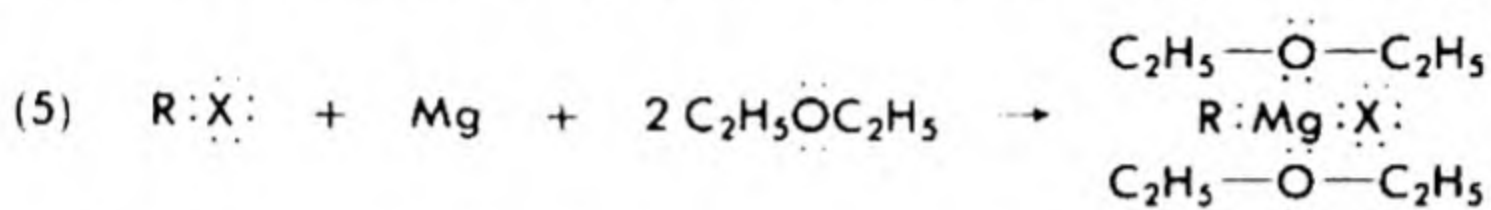


Lewisite was used in the first world war as a poison "gas." It is prepared by addition of arsenous chloride to acetylene (eq. 4) and is both a vesicant and a systemic poison.



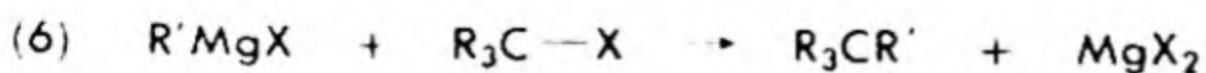
B. Replacement of Halogen by Metal

The direct replacement of a halogen atom by a metal is suitable for the preparation of organometallic compounds of metals intermediate or high in activity, such as magnesium, zinc, lithium and sodium. The metal acts as an electron donor to the halogen atom, after which the alkyl or aryl group rearranges to the electron-deficient metal atom. Solvents with unshared electron pairs coordinate with the metal atom to stabilize the system. An example is the formation of the Grignard reagent (eq. 5).



The preparation of organomagnesium halides was discovered by Victor Grignard, a French chemist, and was named *Grignard reaction* for him. An organomagnesium halide in ether is called a *Grignard reagent*. The ether is important. Distillation of ether from a solution of Grignard reagent leaves a solid solvate containing 2 moles of ether per mole of organomagnesium halide. Grignard reagents usually cannot be prepared in solvents that do not coordinate with divalent magnesium.

Under optimum conditions, yields of Grignard reagents are very high. Primary halides give yields from 90 to 100%, secondary 70 to 90%, and tertiary under 30%, as usually carried out, by addition of the halide to ether covering a slight excess of magnesium turnings. Under optimum conditions, by passing a very dilute ether solution of halide through a column of magnesium powder, *tert*-butyl chloride gives yields of 50-70% of the Grignard reagent. The difficulty in the preparation of tertiary alkylmagnesium halides is the action of the Grignard reagent formed on the as yet unchanged halide. Grignard reagents couple with tertiary halides (as well as with allylic halides and α -haloethers) so dimeric products are obtained. Primary and secondary alkyl halides do not couple as readily with Grignard reagents.



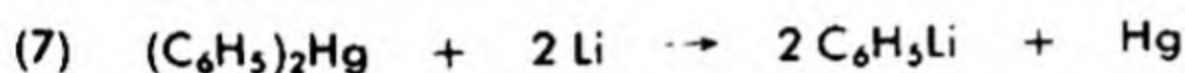
Arylmagnesium bromides and iodides are also prepared in good yields.

The rate of formation of Grignard reagent is greatest from an iodide, least from a chloride. Most alkyl fluorides do not react. The yields are

generally highest from the bromide, lowest from the iodide. Aryl chlorides do not react with magnesium in ethyl ether, but, at the higher temperature of refluxing tetrahydrofuran, do form the Grignard reagent. Vinylmagnesium halides can also be formed in tetrahydrofuran. Alkyl-lithium and aryllithium compounds can be prepared like Grignard reagents. Since lithium is sufficiently more reactive than magnesium, chlorobenzene forms phenyllithium without difficulty. Reactions with lithium do not require ether.

C. Replacement of a Less Active Metal by a More Active Metal

As with metal replacement reactions in inorganic compounds, a metal higher in the electromotive series (adjusted for nonaqueous solvents) replaces another from an organometallic compound. The metal with the higher ionization potential ends up with the electrons as free metal.



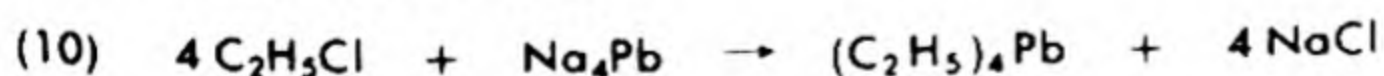
D. Replacement of a More Active Metal by a Less Active Metal

Just as covalent halogen in an organic compound has a charge somewhere between the elementary state and its preferred anionic state, the metal in an organometallic compound is somewhere between the free metallic state and the cationic state. Therefore, the metal which has more tendency to lose electrons prefers the ionic state more than another metal. Thus, in the reaction of an organometallic compound with the salt of a less active metal, an exchange of metals occurs.

Such a reaction is used to prepare organocadmium, organotin, organogermanium, organolead, and organomercury compounds.



Commercially, tetraethyllead is prepared directly from ethyl chloride and sodium-lead alloy.



19-3 TYPICAL ORGANOMETALLIC COMPOUNDS

The most widely used organometallic compounds in synthetic applications are the Grignard reagents, RMgX . A few of these are available commercially, but normally they are prepared just before use.

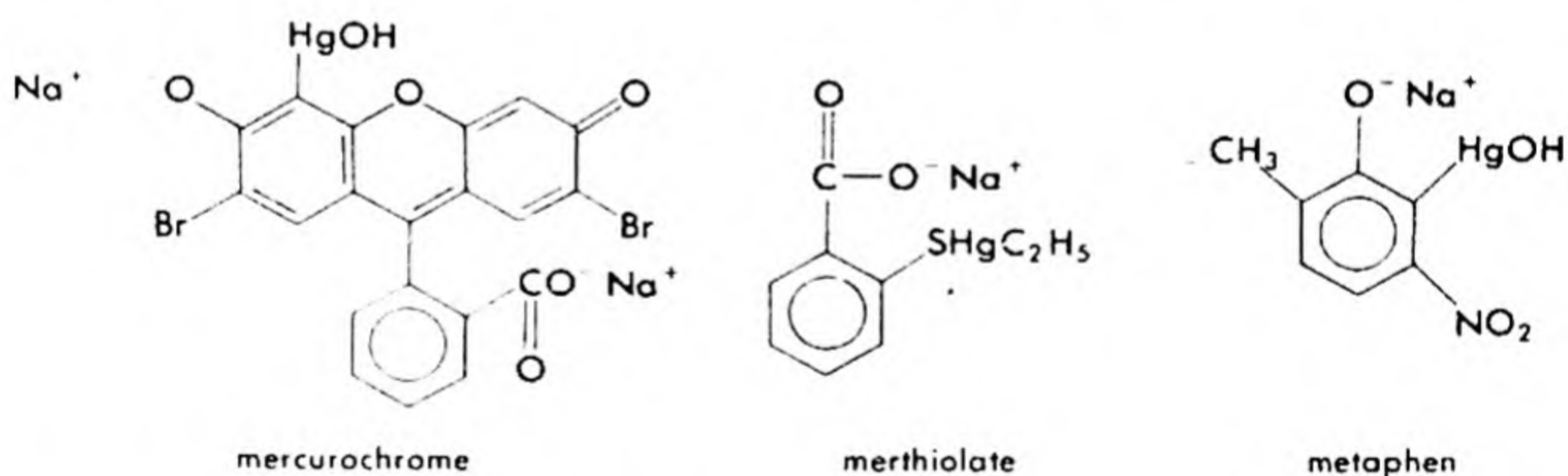
Some organometallic compounds of the heavy metals are commercially important. Tetraethyllead and tetramethyllead, for example, are used in tonnage quantities to improve the antiknock quality of gasoline. The

discovery of the value of tetraethyllead by Thomas Midgley, Jr. in 1922 was an important step in the progress of petroleum utilization and automotive engineering.

Organotin compounds are used as antioxidants in rubber products, both natural and synthetic.

Organomercury compounds as a class are protein precipitants and enzyme poisons highly effective against microorganisms. Treatment of both plants and animals is confined to topical (surface) treatment, since such compounds are as damaging to the host as to the parasite internally. Phenylmercuric acetate formulations and related salts are effective weapons against rots, mildews, blights, and molds that attack flowering shrubs, orchard trees, seeds, and bulbs. Their use against vegetable diseases is prevented because of danger of poisoning the vegetable consumer by residues of the fungicide left on edible portions of the vegetable.

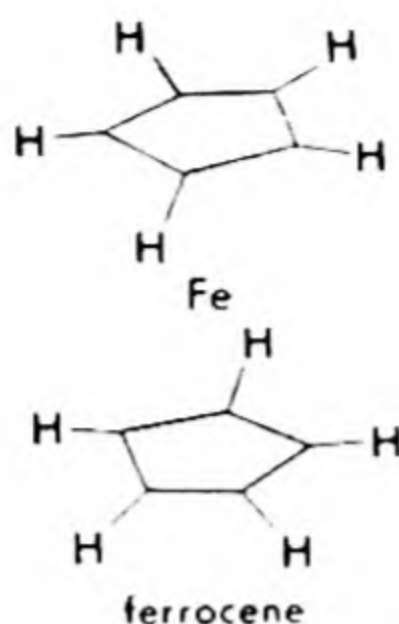
A few organomercury compounds mild enough to be used on open cuts and wounds have been developed. Mercurochrome, disodium dibromohydroxymercurifluoresceinate, was long popular as a germicide until it was shown to be too mild to be effective. Merthiolate, sodium *o*-ethylmercurithiobenzoate, and metaphen, sodium 2-hydroxymercuri-3-nitro-6-methylphenoxide, are much more effective germicides.



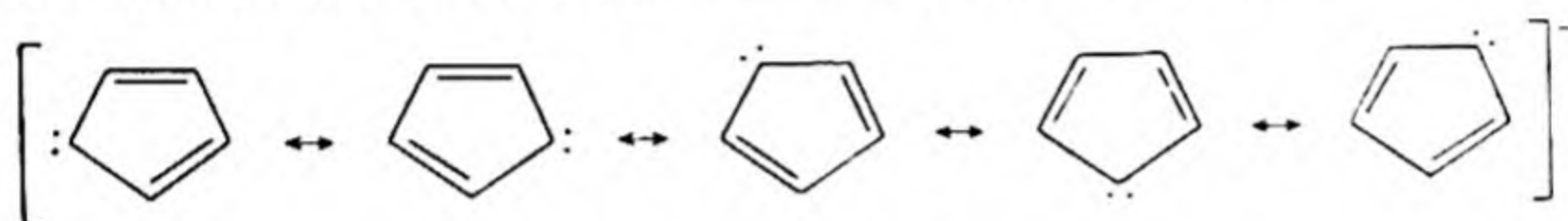
The various uses of other organomercury compounds and of organo-arsenic compounds were mentioned in §19-2A.

A. Sandwich Compounds

Besides the classical organometallic compounds considered heretofore, there are certain interesting organometallic types of recent discovery. Ferrocene (ferrous bis(cyclopentadienide)) is an interesting example from a theoretical viewpoint, since it illustrates in a new way a number of important principles. In the formula, below, the hydrogen atoms are shown to emphasize that the hydrocarbon portions have one less hydrogen atom each than cyclopentadiene. The valence between the hydrocarbon portions and the iron atom is left purposely indefinite for the moment.



The cyclopentadienide ion (below and Fig. 19-1) has a six-electron mesomeric system with π orbitals very similar to those of benzene. The only differences are the number of atoms over which the electron system is distributed and the resultant overall charge of the system.



cyclopentadienide ion, valence-bond structures

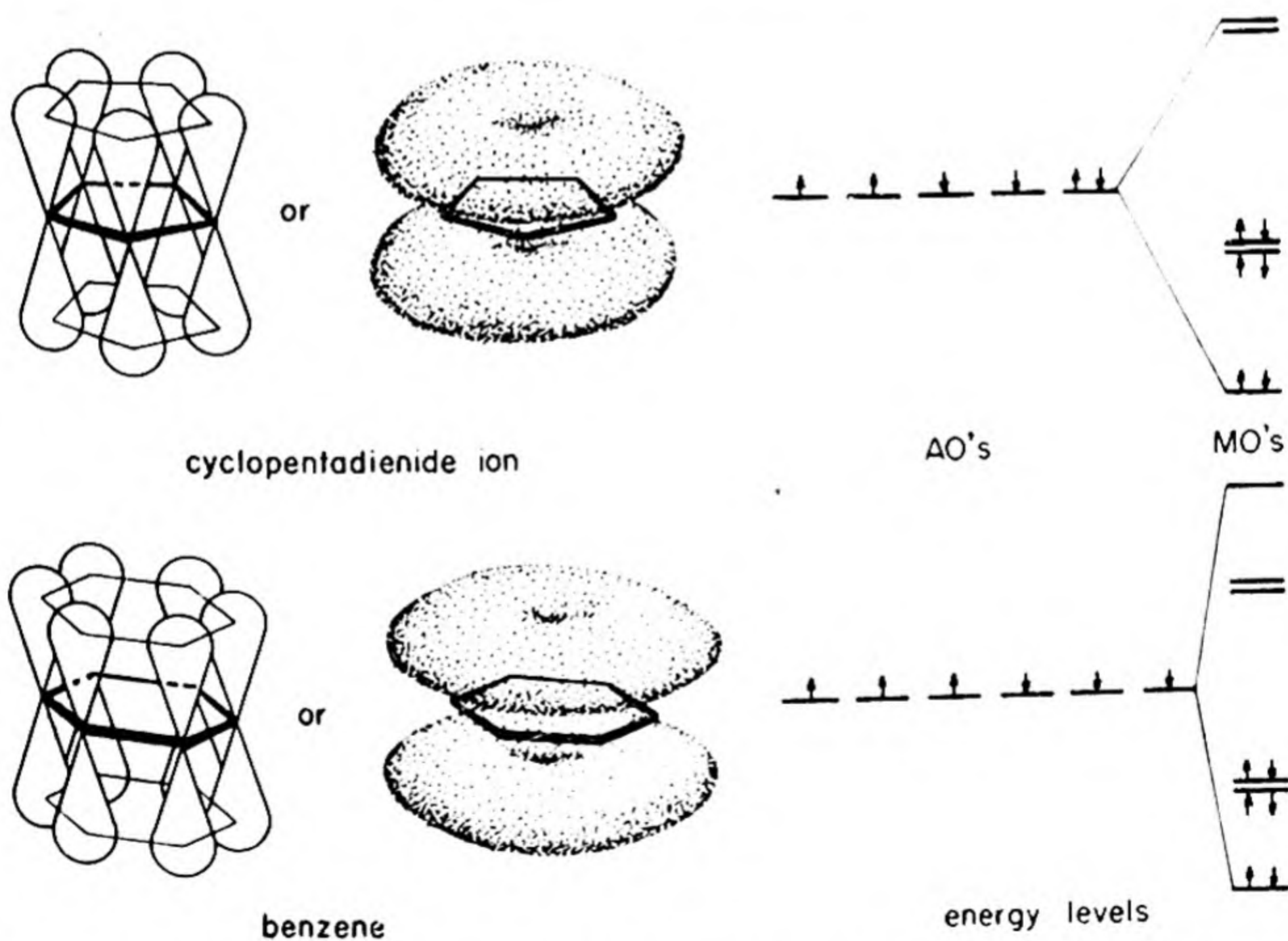
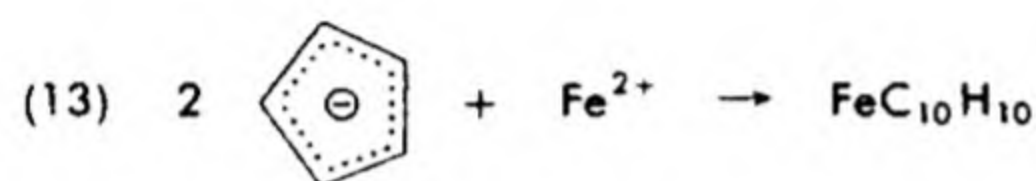
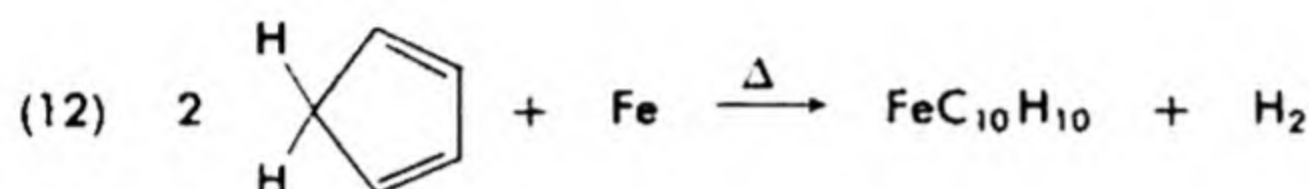
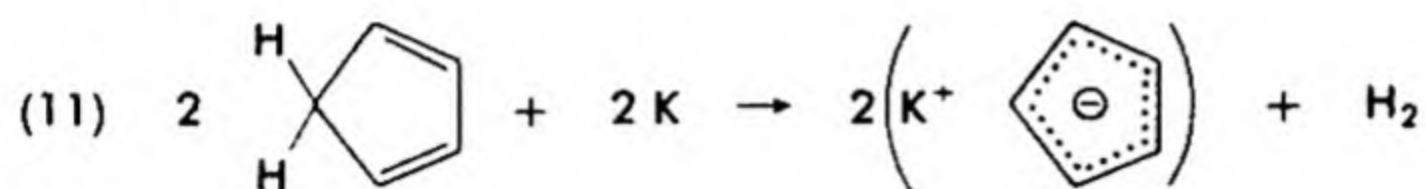
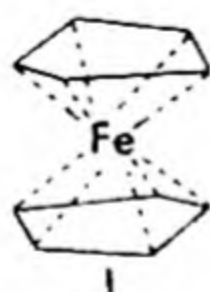


Fig. 19-1. Similarity between MO of Cyclopentadienide Ion and MO of Benzene. Refer to Fig. 7-6 for diagrams of highest bonding orbitals.

A consequence of the resonance stabilization of the cyclopentadienide ion is that it is readily prepared by some metallation reactions. Thus, cyclopentadiene reacts with potassium under benzene to form potassium cyclopentadienide (eq. 1) or with hot, activated iron to form ferrocene (eq. 12). The potassium salt reacts with ferrous chloride also to give ferrocene (eq. 13).

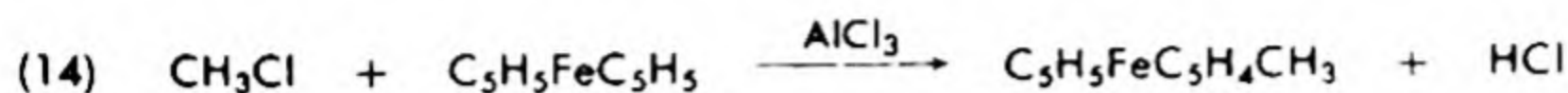


These reactions may suggest that ferrocene is an ionic compound. However, solutions of ferrocene do not dissociate into ferrous ions and cyclopentadienide ions. A further suggestion has been made that ferrocene is a π complex between the ferrous ion and the π -orbitals of the two cyclopentadienide ions. This is in agreement with x-ray diffraction data which indicate that ferrocene is a "sandwich" with the iron atom as filling between two "slices" of cyclopentadienide ion. Other chemists have suggested more or less covalent character due to overlap between d atomic orbitals of the ferrous ion and the p atomic orbitals of the cyclopentadienide ions. All of these viewpoints have certain elements of truth; the compound is ionic in the sense that separate entities with electronic charges can be dissected for discussion purposes and covalent in the sense that a definite bond holds the ferrous ion to the cyclopentadienide ions too tightly for detectable dissociation. As to the exact nature of the bonding orbitals, there is ample room for discussion yet. The compound is thus generally represented as I, a sufficiently vague formula to allow a number of bonding possibilities.



The aromatic character of the cyclopentadienide portions of the compound is well exemplified by typical aromatic substitution reactions, for

example, alkylation (eq. 14). The unusual bonding stability is indicated by the fact that neither the aluminum chloride nor the hydrogen chloride



decomposes the ferrocene or the alkylated ferrocene.



Similar "sandwich compounds" involving other metals and other hydrocarbons with a cyclopentadiene ring, such as indene, are known.

B. Organometalloids

Some organosilicon compounds, such as those given below, are commercially important raw materials for silicones (Chapter 45).

CH_3SiCl_3
methyltrichlorosilane

$(\text{CH}_3)_2\text{SiCl}_2$
dimethyldichlorosilane

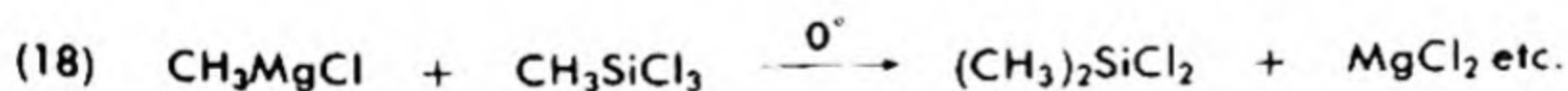
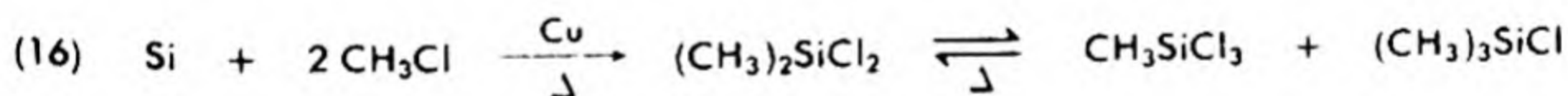
$(\text{CH}_3)_3\text{SiCl}$
trimethylchlorosilane

$\text{C}_2\text{H}_5\text{SiCl}_3$
ethyltrichlorosilane

$(\text{C}_2\text{H}_5)_2\text{SiCl}_2$
diethyldichlorosilane

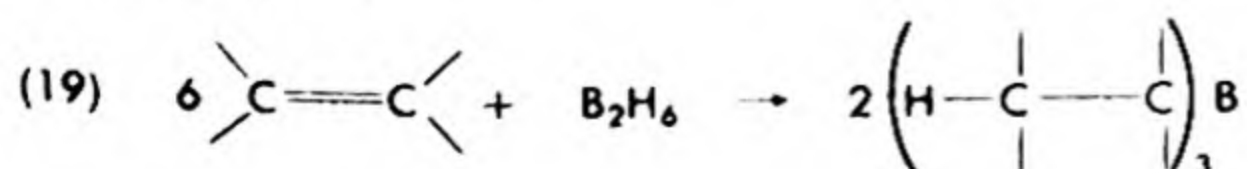
$(\text{C}_2\text{H}_5)_3\text{SiCl}$
triethylchlorosilane

These compounds are prepared by the direct action of silicon on alkyl halides in the presence of copper powder (outline 16) or by reaction of alkylmagnesium halides with silicon tetrachloride (eqs. 17 and 18).

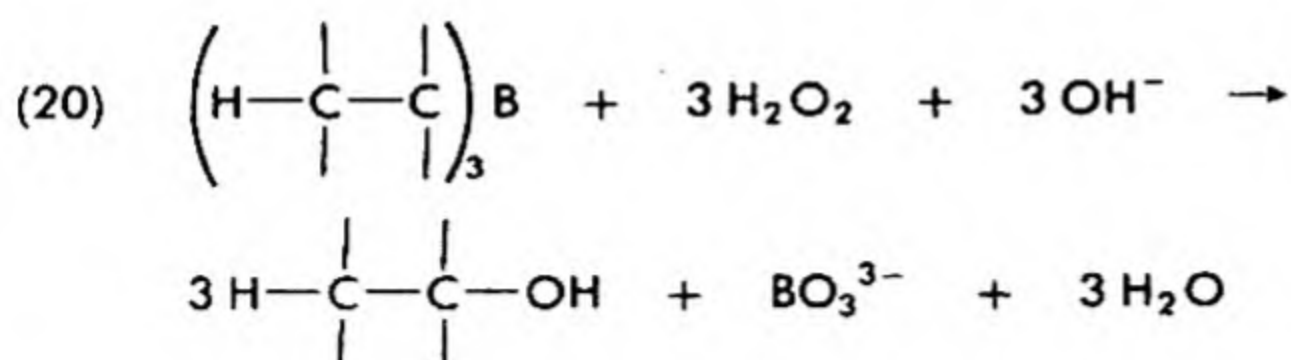


Mixtures of compounds result which are readily separated by distillation. The use of Grignard reagents for these reactions led to the first successful industrial control of Grignard reactions.

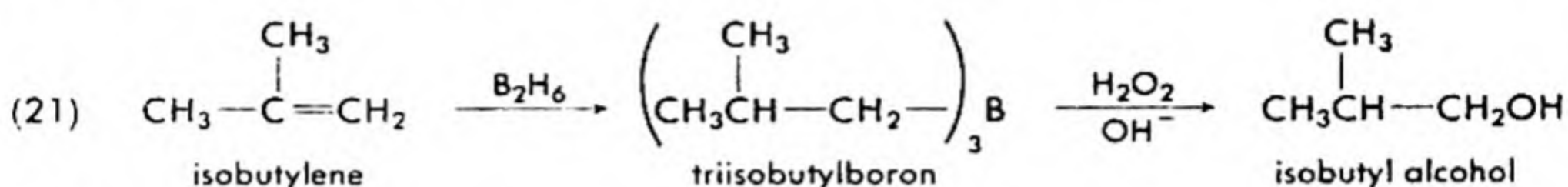
(1) *Hydroboration* Organoboron compounds are intermediates in some useful new methods for preparing alcohols. The organoboron compounds are most easily prepared by *hydroboration*, the addition of diborane to olefins (eq. 19).



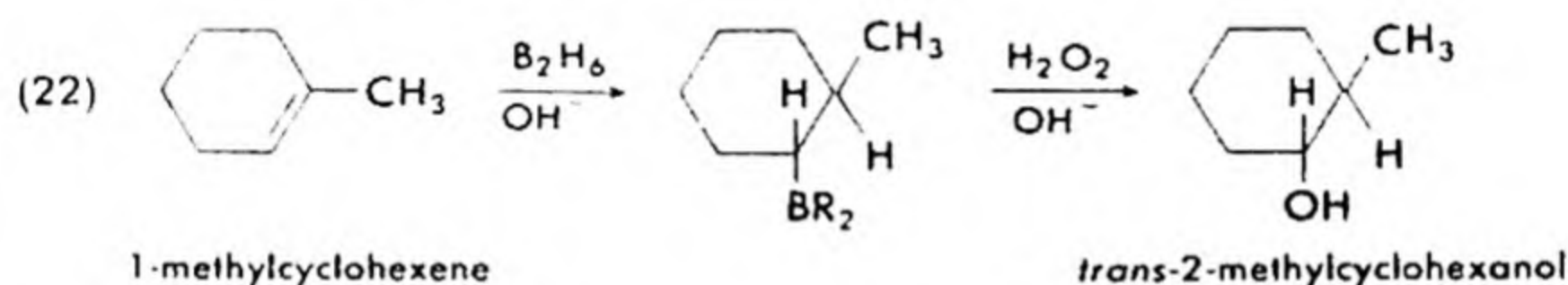
Treatment of the organoboron derivatives with hydrogen peroxide yields the alcohols. The importance of this sequence as a synthetic



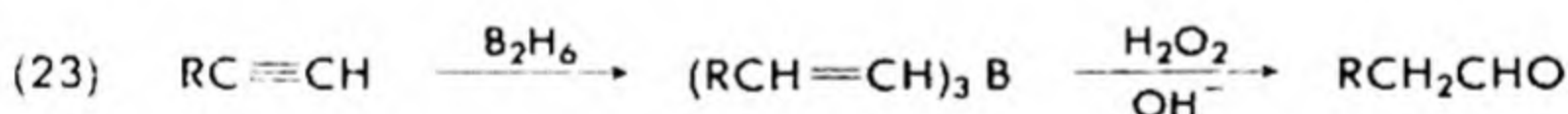
method is the mode of addition of the diborane (borethane, boron hydride). This compound adds largely *contrary to Markovnikoff's rule*; thus the alcohol finally produced has the hydroxy group on the less substituted carbon atom of the original C=C linkage (outline 21).



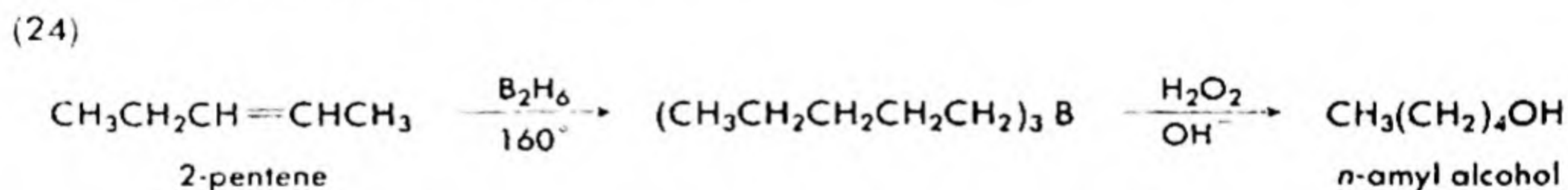
Hydroboration is a *cis* addition process. The oxidation also goes with retention of configuration. Thus, the overall process results in the formation of an alcohol in which the stereochemical relationship of these groups is known (e.g., outline 22).



Addition to acetylenes leads, after oxidation, to aldehydes, via the vinylborane and vinyl alcohol.

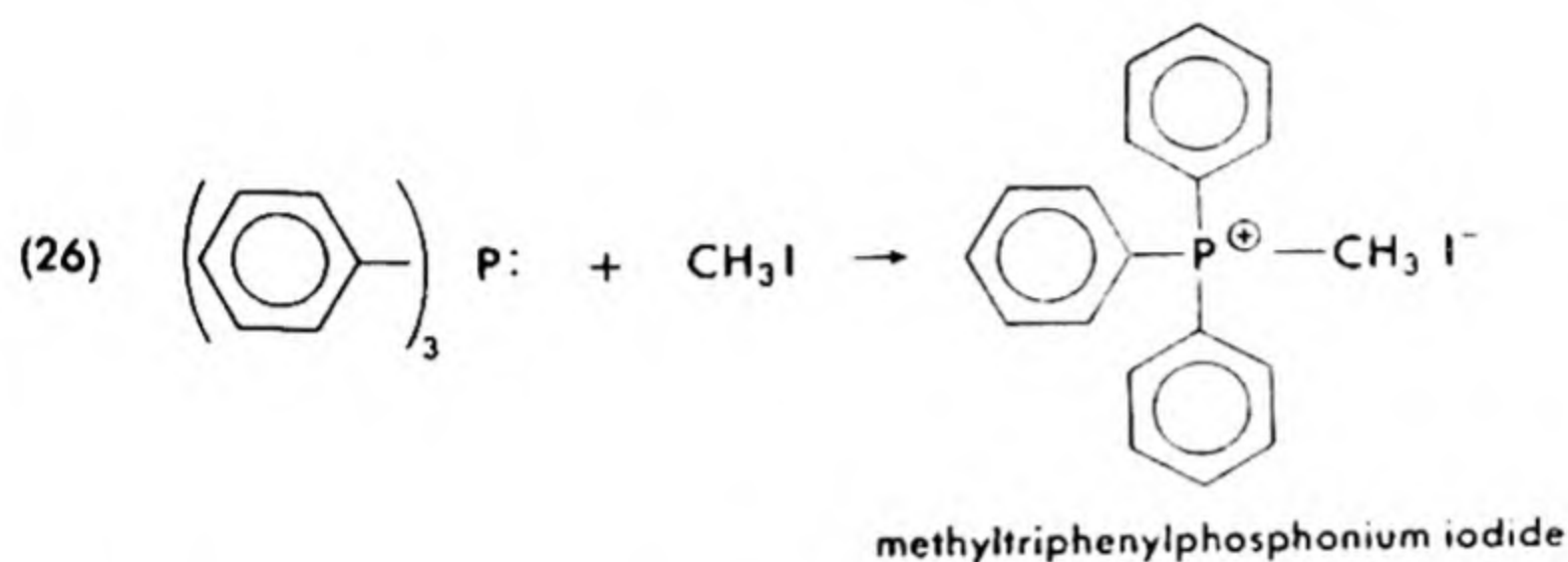
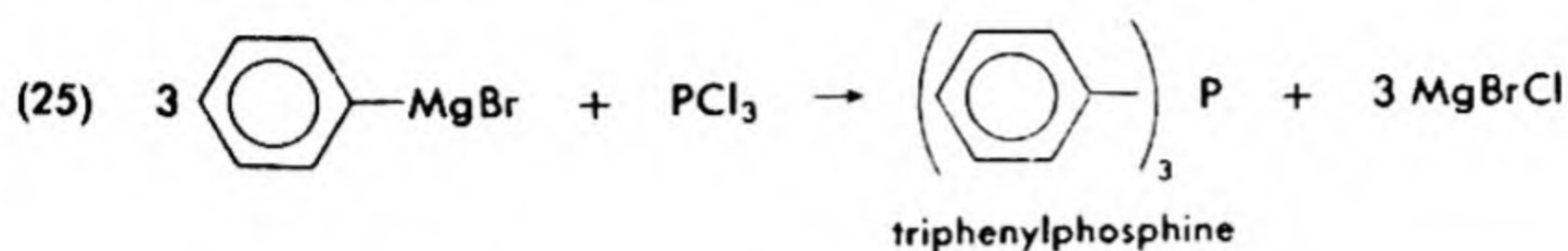


The addition of diborane to olefins is reversible. This has the interesting application that heating an internal olefin with diborane leads to the predominant formation of a primary alcohol (or two alcohols if the olefin has an unsymmetrical chain).

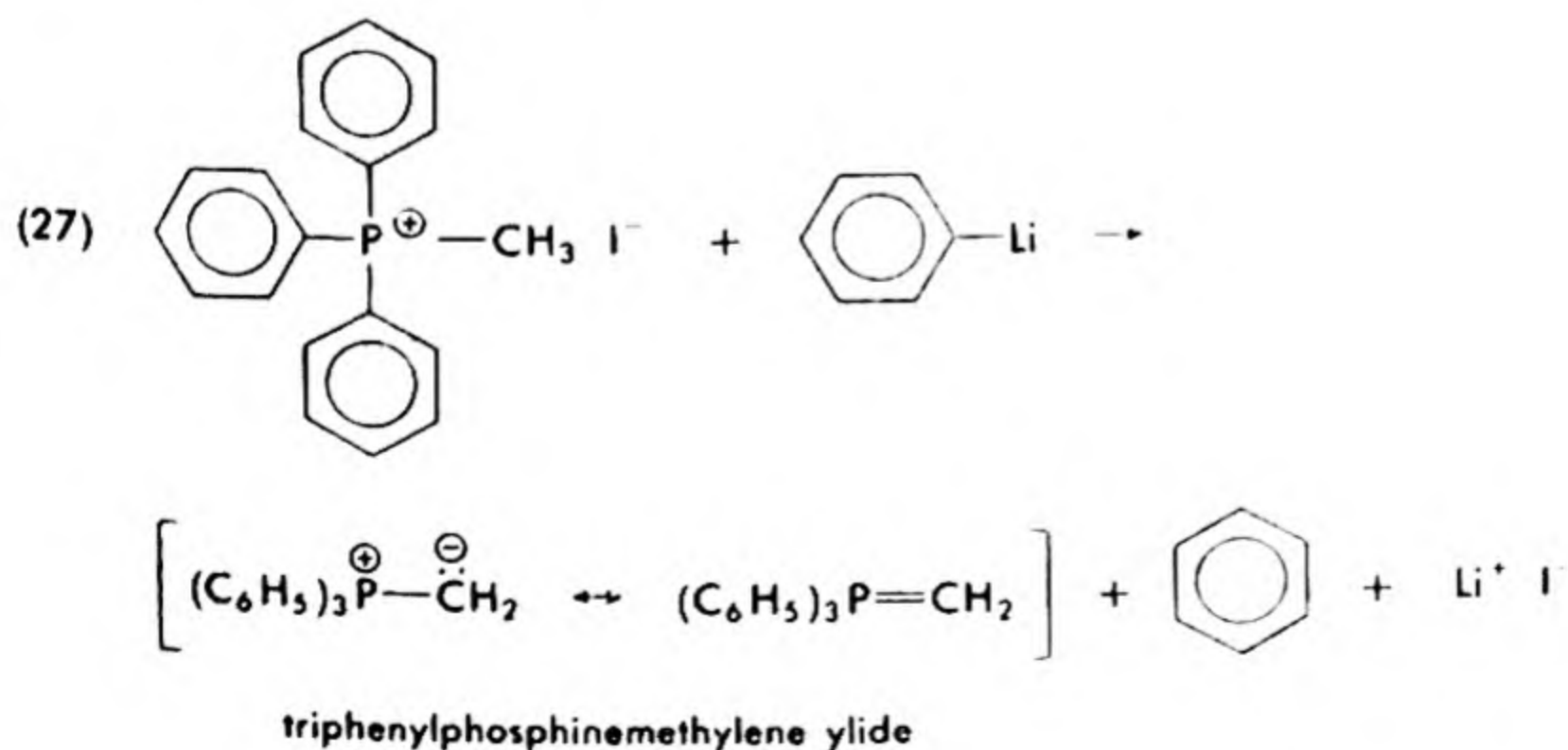


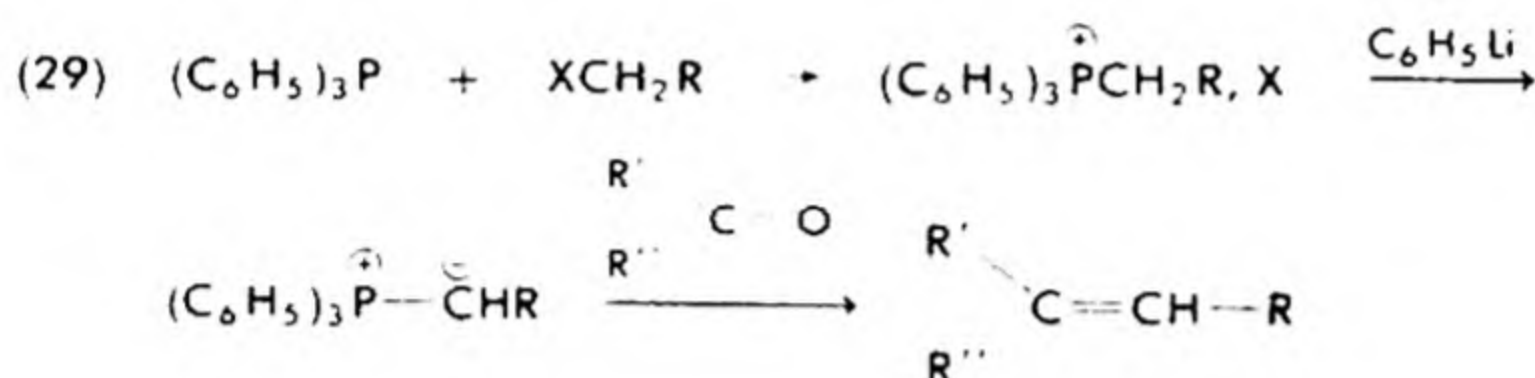
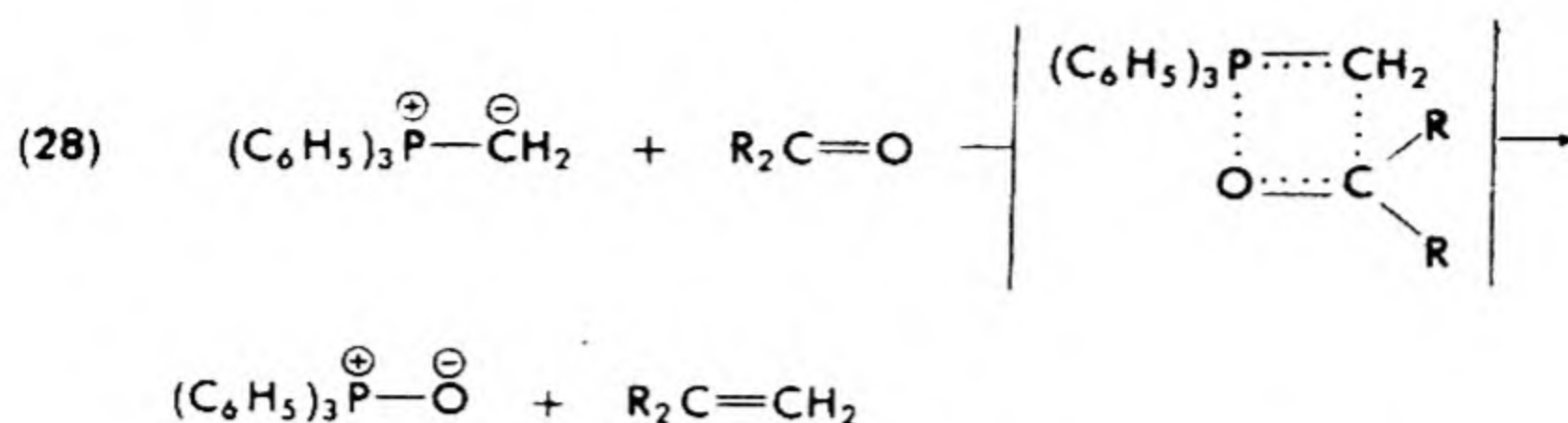
(2) *Organophosphorus Compounds; The Wittig Synthesis of Olefins.* Trialkyl- and triarylphosphorus compounds are prepared by the reaction of an excess of a Grignard reagent with phosphorus trichloride (eq. 25). Reaction with limited amounts of Grignard reagent may lead to alkyl-

dichlorophosphines, R_2PCl_2 , and dialkylchlorophosphines, R_2PCl . Phosphines are nucleophilic, since they are similar in nature to amines. Thus, triphenylphosphine reacts with methyl iodide to give methyltriphenylphosphonium iodide (eq. 26). This material, like the corresponding qua-



ternary ammonium compound, is salt-like in character. When methyltriphenylphosphonium ion is treated with a strong base, such as phenyllithium, a proton is lost from the methyl group to give an *ylide* with the two valence-bond structures shown in eq. (27). This ylide is named triphenylphosphinemethylene. Presumably the ylide is stable because of the ability of phosphorus to accommodate ten electrons in its valence shell. Treatment of the ylide with an aldehyde or ketone results in the formation of an olefin (eq. 28). This is called the *Wittig synthesis* after its originator. When higher alkyl halides are used, internal olefins are produced (outline 29).





19-4 SPECIAL HANDLING PROBLEMS

Organometallic compounds provide hazards peculiar to themselves. Some are highly reactive; all are foreign to biological systems.

A. Physiological Hazards

As a class, organometallic compounds are highly toxic. The vapors of volatile compounds are very poisonous, especially those of compounds of zinc, lead, and mercury. Many organometallic compounds can cause severe blistering of the skin. Organomercury compounds are especially strong vesicants. Organolead compounds can cause chronic or acute lead poisoning by absorption through the skin. Gasoline containing tetraethyllead should not be used for cleaning because contact of the lead compound with the skin, as well as inhalation of the vapors, may cause either acute or chronic lead poisoning. Body cells decompose organometallic compounds, forming inorganic salts, many of which attack enzymes.

B. Flammability

Organometallic compounds of alkali metals, metals below magnesium in the alkaline earth group, and zinc are pyrophoric. That is, they take fire immediately upon contact with the air. These compounds and their solutions must be handled under inert atmospheres. Grignard reagents and some organolithium compounds are not dangerous in this respect, although they do react with oxygen, thus diminishing the yield of desired products. In any case, exclusion of oxygen is a matter of expediency.

C. Sensitivity to Atmospheric Constituents

The sensitivity of many organometallic compounds to constituents ordinarily present in the atmosphere, besides presenting a definite hazard

in some instances as above, calls for special provisions in their utilization. Even organometallic compounds which are not spontaneously flammable may react with oxygen to form metallic alkoxides and alkyl peroxides of little value.

Other atmospheric constituents to which these reagents are sensitive are moisture and carbon dioxide. The more active the metal the more sensitive the organometallic compound. Thus, for many organometallic compounds a dry, inert atmosphere such as nitrogen is needed. For Grignard syntheses, the cost and bother of furnishing such an atmosphere may be more than the value of the reagent lost by reaction with air. Hence, often the only precaution taken in such syntheses is the exclusion of moisture. However, if the Grignard reagent must be heated under reflux for any extended period of time, the loss of reagent by atmospheric oxidation is substantial.

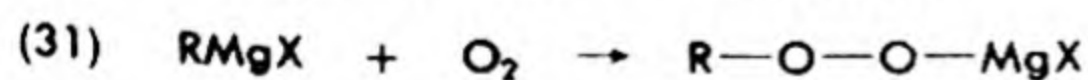
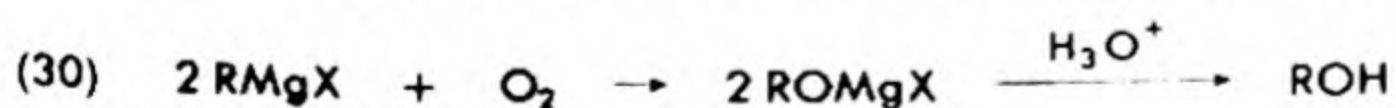
No problems arise in atmospheric contact with organomercury, organo-lead, or other unreactive organometallic compounds. Some of these are inert even toward weak acids (eq. 1).

19-5 CHEMICAL REACTIONS

As synthetic intermediates, the most important organometallic compounds are Grignard reagents. These are emphasized heavily in the ensuing discussion. The formulation RMgX is used, although a more accurate representation is $\text{RMgX} \cdot 2(\text{CH}_3\text{CH}_2)_2\text{O}$, in which the magnesium is tetrahedral and has a completed octet.

A. Reactions with Oxidizing Elements

The reaction with oxygen has been mentioned as detrimental in the use of more active organometallic compounds. The reaction of *alkyl* Grignard reagents with oxygen has limited synthetic use in the preparation of alcohols (outline 30), while *aryl* Grignard reagents give very poor yields of phenols. The oxidation reaction proceeds through the hydroperoxide salt (eq. 31), which is then reduced by another mole of reagent (eq. 32). The reaction of aryl Grignard reagents fails because the second step does not proceed well. One can use an alkyl Grignard reagent to reduce $\text{ArO}-\text{O}-\text{MgX}$ compounds to phenols in good yield.

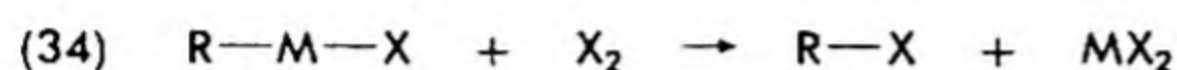


The reaction of Grignard reagents with elemental sulfur proceeds to give thiols or thiophenols (outline 33).



As has been mentioned, organometallic compounds low in reactivity do not react with oxygen. However, free halogens are very powerful oxidizing agents, hence even relatively inert organometallic compounds are attacked by chlorine and bromine.

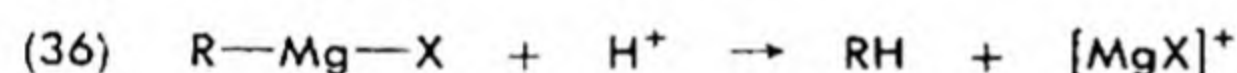
The halogenolysis reaction has little preparative value, but can be used to establish the position of metallic atoms on an organic molecule, since the halogen atom takes the position of the metal atom removed. The method is most useful when applied to organometallic compounds that do not react with carbon dioxide, which gives more reliable results with the more active organometallic compounds.



B. Reactions with Acidic Compounds

Strong acids are much more active than oxygen in reacting with organometallic compounds, but fall below halogens in reactivity. Thus, even nitric acid fails to cleave some organomercury compounds readily cleaved by bromine.

Active organometallic compounds can be considered strong bases involving virtual carbanions. The nearly complete lack of acidity in hydrocarbons (§10-2) means that a carbanion is a very efficient hydrogen-ion trap. Water, for example, attacks a Grignard reagent to give a hydrocarbon molecule (eq. 35). The remaining magnesium compound reacts further with the water. The reaction is catalyzed by acids.

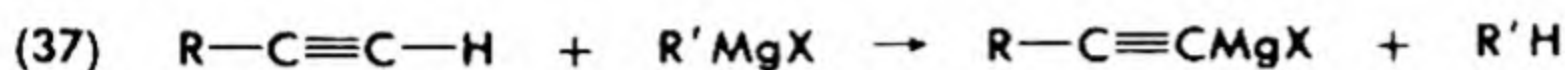


Potentially acidic compounds which form moderately stable anions protonate Grignard reagents. This means that any compound which has hydrogen on halogen, oxygen, sulfur, nitrogen, or even certain carbon atoms (e.g. 1-alkynes and cyclopentadienes), such as water, alcohols, mercaptans, primary and secondary amines, simple amides, alkynes, fatty acids, mineral acids, and phenols, decompose Grignard reagents to form a hydrocarbon and the salt of the active hydrogen compound.

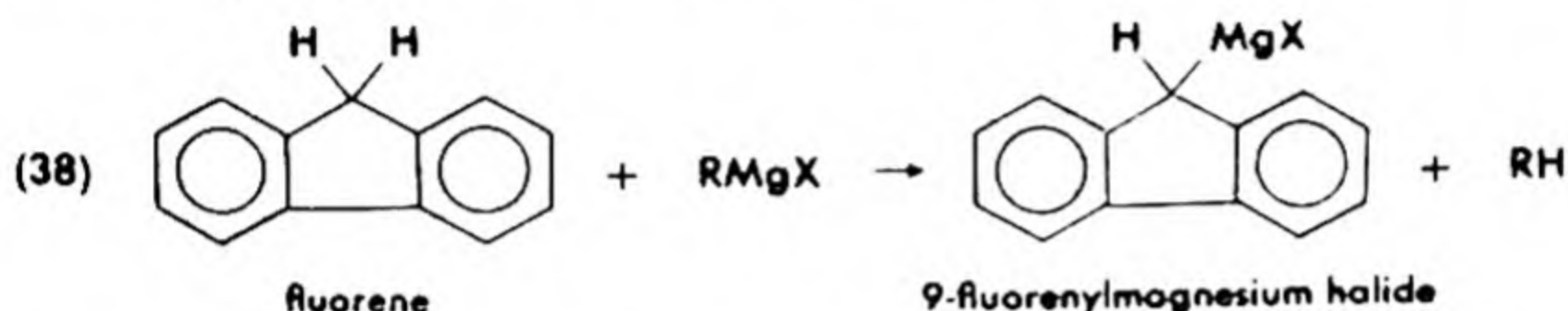
Of all these reactions, only exchange reactions involving active hydrogen on carbon atoms have any general preparative value. Hydrolysis with deuterium oxide can be used to introduce deuterium into hydrocarbons. Otherwise, the rest are reactions that trap the unwary student who attempts to synthesize Grignard reagents with hydroxy groups or amino groups in them or who expects Grignard reagents to react at carbonyl groups when there are such acidic groups in the same molecules. Since

this is not possible, the student must be on guard against any such *faux pas* in problem or laboratory work.

An example of the use of an exchange reaction to prepare an acetylenic Grignard reagent, otherwise very difficult to obtain because of the difficulty of preparing the corresponding halide, is the reaction represented in eq. (37).



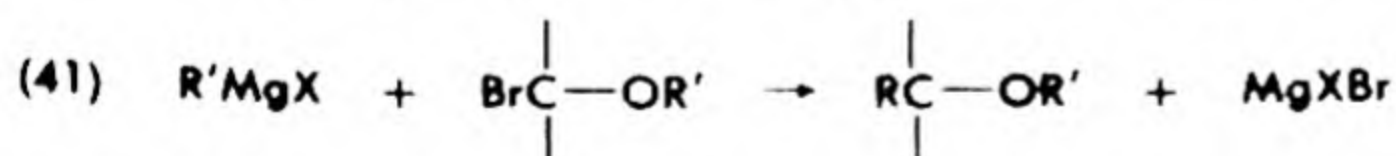
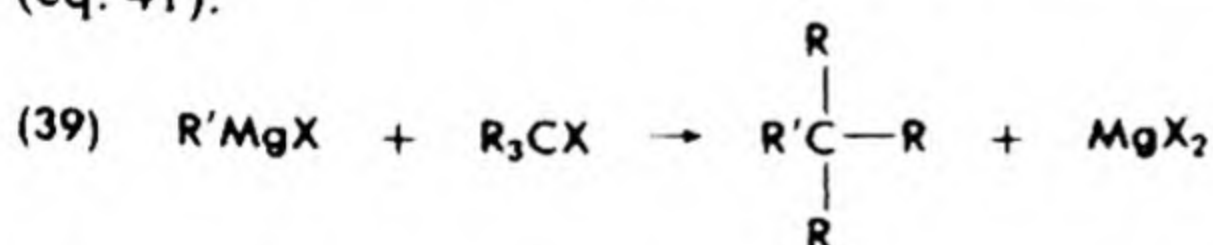
Another example of metallation of a hydrocarbon is the preparation of a fluorenylmagnesium halide from fluorene (eq. 38).



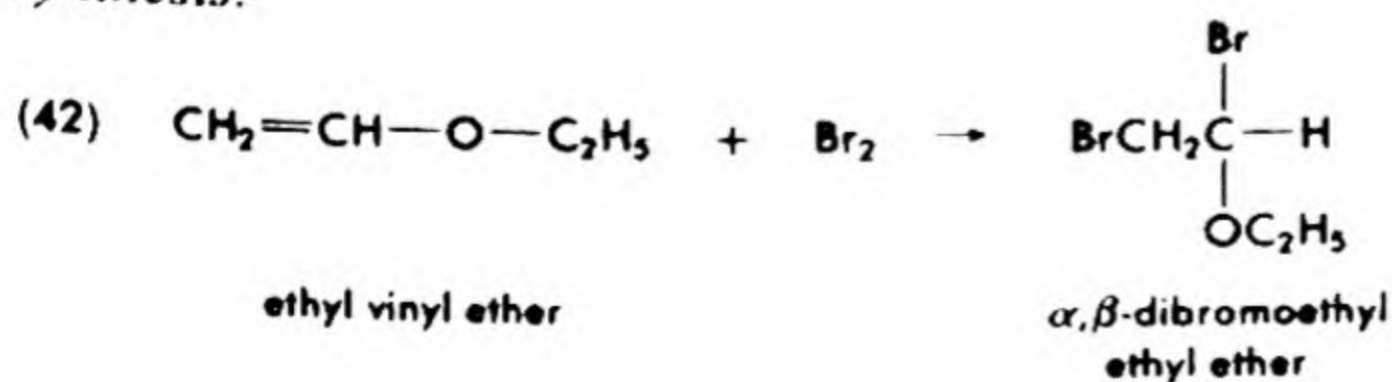
C. Reactions with Halides and Sulfates

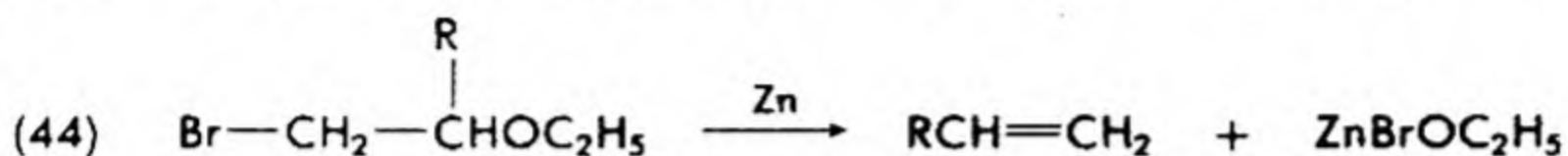
Of all the reactions of Grignard reagents, the reaction with an alkyl halide or sulfate, called *coupling*, is the slowest. Were this not the case, a Grignard reagent could hardly be prepared at all. The reaction is subject in an immoderate degree to side reactions, the most extensive of which is disproportionation. This results in formation of units of alkene and alkane of the same size as the original alkyl groups, rather than coupled products containing both groups.

Coupling is useful synthetically only with three types of halides. These are tertiary halides, (eq. 39), allylic halides (eq. 40), and α -haloethers (eq. 41).

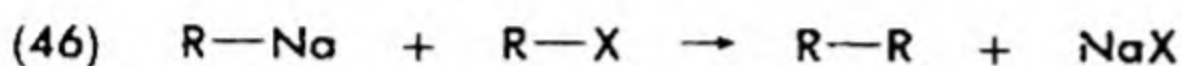
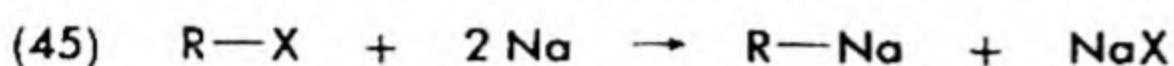


The latter reaction is used for the synthesis of α -olefins through the *Boord synthesis*.



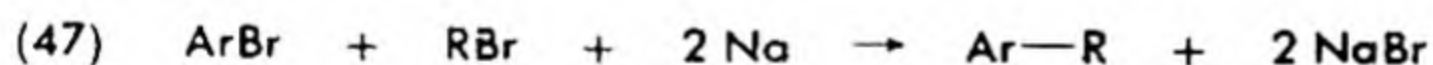


Another coupling reaction which involves an organometallic compound is the *Wurtz reaction*. In this reaction no attempt is made to isolate an intermediate organometallic product, but the proportions of reagents are such as to promote coupling. Nevertheless, the steps of the reaction are doubtless those represented in eqs. (45) and (46).

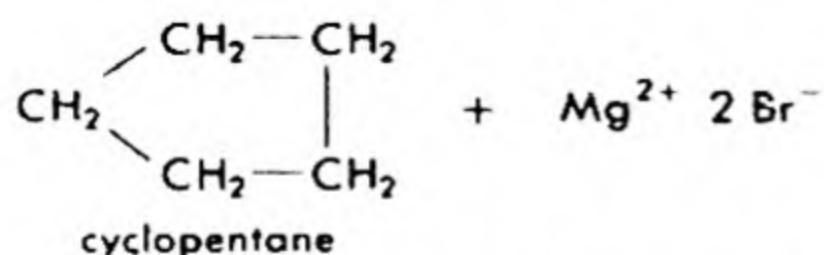
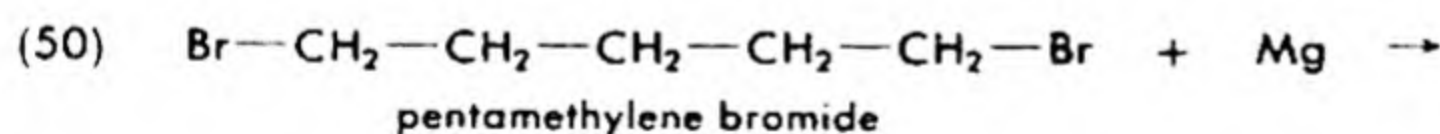
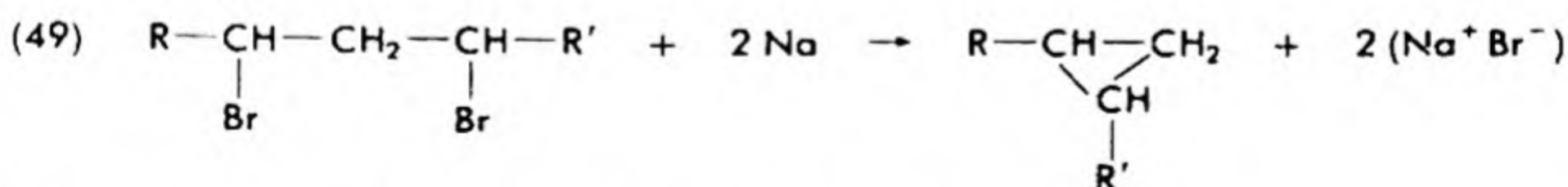
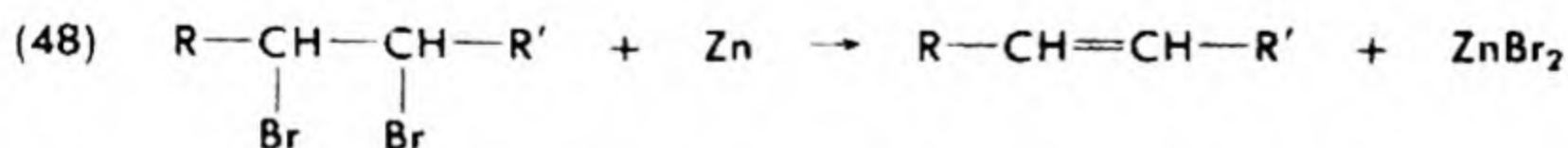


The Wurtz reaction is sometimes a good way to synthesize symmetrical compounds with nonacidic and nonreducible groups. However, reactions of mixed halides with sodium give all possible products. Except when there are directive influences tending to offset the statistical probability, the maximum yield of mixed coupling product is 50%.

In reactions between aryl halides, alkyl halides, and sodium, there is just such a directive influence. This is the unreactivity of an aryl halide to nucleophilic displacement. Advantage is taken of the preference for mixed coupling between aryl halides and alkyl halides in the *Wurtz-Fittig* reaction.



Other reactions of preparative interest are olefin formation and cyclizations brought about by action of active metals on dihalides (see §13-1 and §13-4C).



Three-carbon to six-carbon rings are particularly easy to form by internal coupling.

SUPPLEMENTARY READINGS

- Bennett, M. A., "Olefin and Acetylene Complexes of Transition Metals," *Chem. Rev.*, **62**, 611 (1962).
- Brown, H. C., *Hydroboration*, Benjamin, New York, 1962.
- Kharasch, M., and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Englewood Cliffs, N. J., 1954.
- Maercker, A., "The Wittig Reaction," *Org. Reactions*, **14**, 270-490 (1965).
- Zweifel, G., and H. C. Brown, "Hydration of Olefins, Dienes and Acetylenes via Hydroboration," *Org. Reactions*, **13**, 1-54 (1963).

QUESTIONS AND PROBLEMS

1. What is an organometallic compound? What precautions are necessary in handling one?
2. What is a Grignard reagent? What precautions are necessary to assure a good yield in a Grignard synthesis?
3. List only the compounds which are organometallic from those given below. Write their structural formulas.

- | | |
|--------------------------|----------------------------|
| a. sodium benzoate | f. ethyl sodioacetoacetate |
| b. silver acetylide | g. phenyllithium |
| c. diisobutylzinc | h. allylmagnesium chloride |
| d. 2-chloromercuriphenol | i. dimethyldichlorosilane |
| e. aluminum isopropoxide | j. tetramethyllead |

4. Write equations for the reactions that occur between the reagents in the mixtures listed below.

- | | |
|--|--|
| a. <i>n</i> -propylmagnesium bromide and ethanol | f. allylmagnesium chloride and cadmium chloride |
| b. phenylmagnesium bromide and sulfur | g. boron trichloride and benzylmagnesium chloride |
| c. isopropylmagnesium bromide and acetic acid | h. phosphorus trichloride and excess phenylmagnesium bromide |
| d. 1,4-bis-acetoxymethylbenzene and iodine | i. norbornene and diborane |
| e. <i>n</i> -butylmagnesium bromide and calcium | j. triphenylphosphinebenzylidene and methyl ethyl ketone |

5. Show how the following compounds can be prepared from the suggested starting materials and inorganic reagents. Use structural formulas for organic compounds. Indicate essential special conditions.

- | | |
|--|--|
| a. triphenylsilyl chloride from benzene | c. <i>p</i> -tolylmercuric acetate from toluene and acetic acid |
| b. propylidenecyclopentane from benzene, propylene, and cyclopentanone | d. cyclohexylmethanol from benzene, cyclohexanone, and methyl iodide |

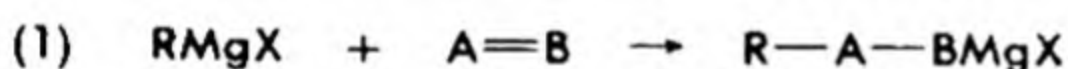
20

Nucleophilic Displacements and Additions in Unsaturated Systems

III. Grignard Syntheses and Hydride Reductions

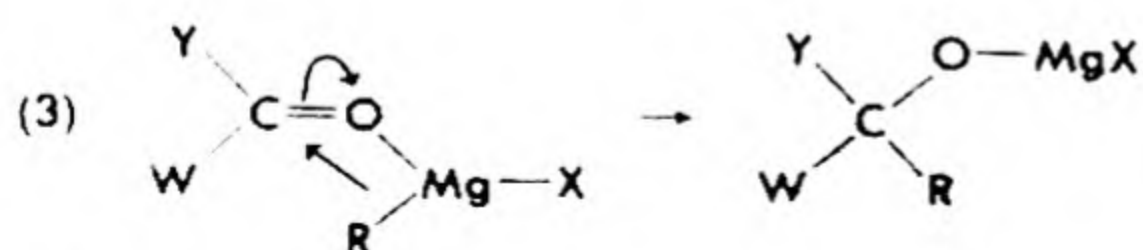
20-1 GRIGNARD SYNTHESSES AND SIMILAR REACTIONS BY OTHER ORGANOMETALLIC COMPOUNDS

Most of the synthetically important reactions of Grignard reagents are those with polar unsaturated groups. The reactions can be generalized as represented in eq. (1). The group A might be a carbon atom with its other two valences satisfied by hydrogen atoms or alkyl groups, etc., and B might represent an oxygen, sulfur, or nitrogen atom.

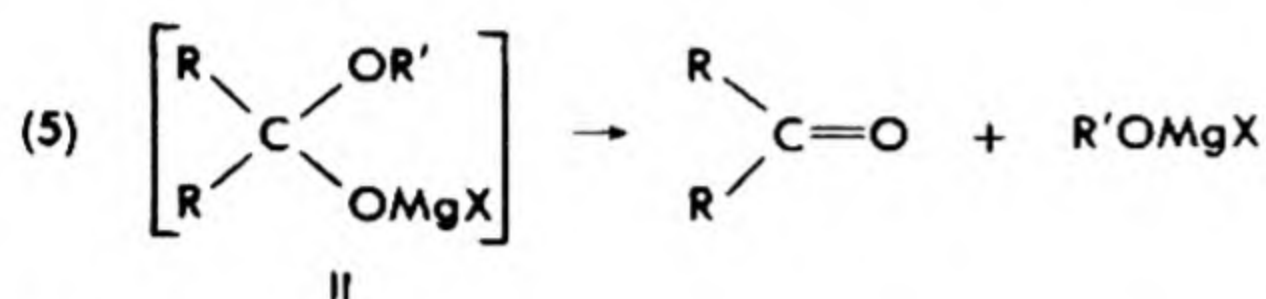
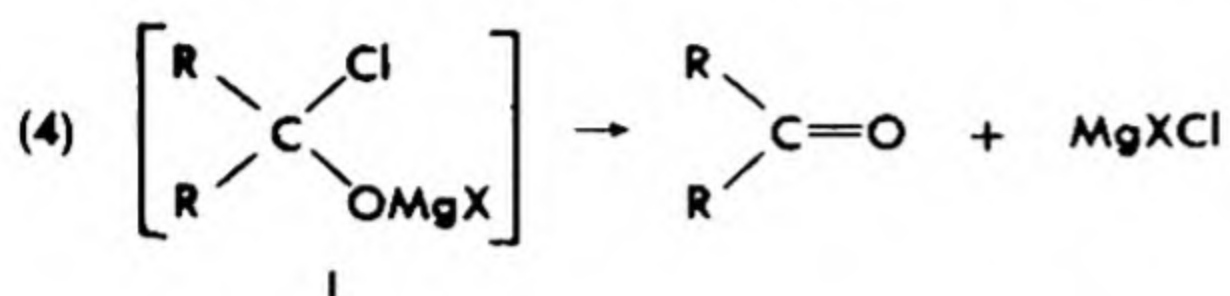


A. Mechanism of Grignard Syntheses by Addition

A Grignard reagent acts on a polar unsaturated bond in much the same way as any other nucleophile. The magnesium atom probably augments the electrophilic character of the active carbon atom (eq. 2) by coordination with the hetero atom. This complex now may rearrange with the anionoid alkyl or aryl group migrating to the cationic carbon atom (eq. 3).



Whether W or Y splits off the molecule, along with the halomagnesium ion, depends on the same considerations that govern removal of HW or HY under similar circumstances. For example, groupings such as I and II are unstable and thus eliminate the indicated molecules or ions. Since

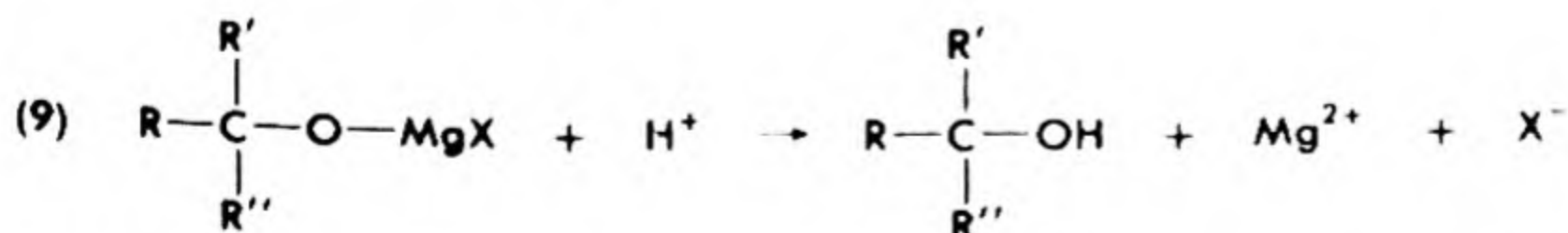
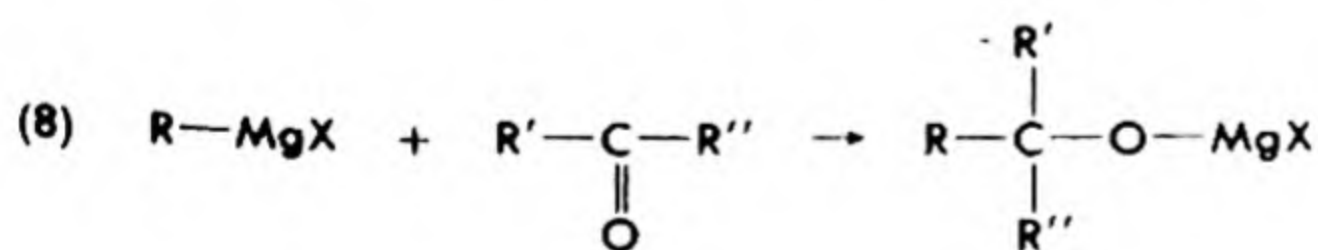
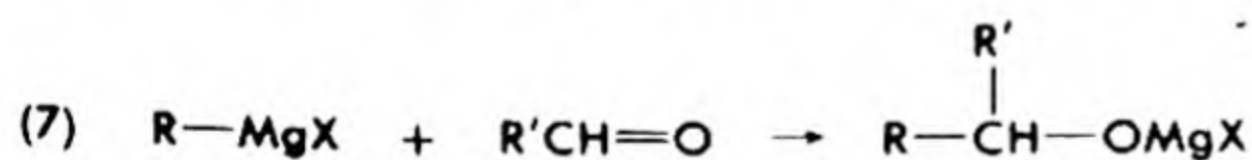
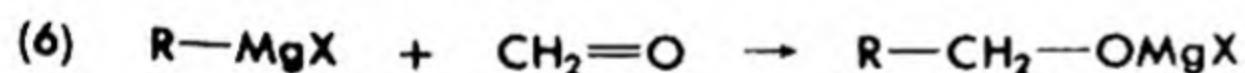


these eliminations occur rapidly, leaving reactive aldehydes or ketones in the reaction mixture, these are then attacked further by the reagent.

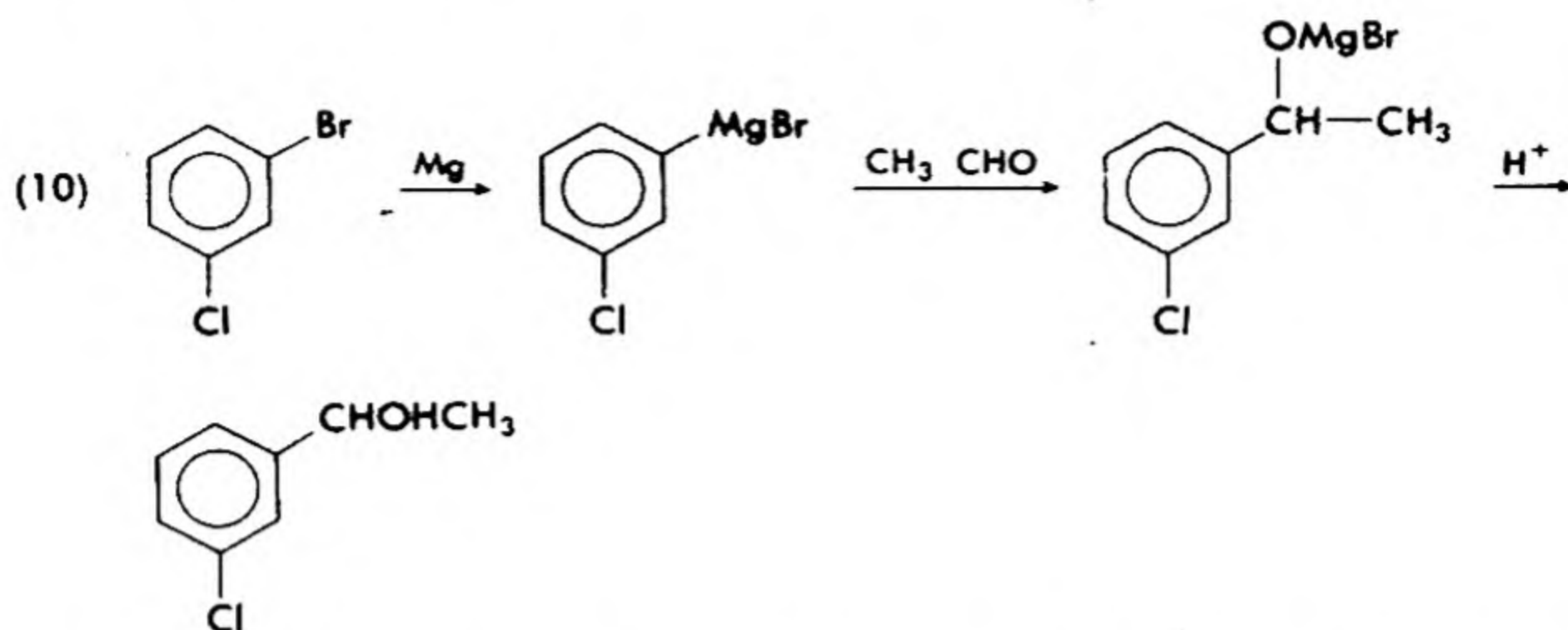
If the product of eq. (3) is stable, the desired metal-free organic compound can be liberated by hydrolysis with dilute acid. If the compound is sensitive to acid, aqueous ammonium chloride is used.

B. Aldehydes and Ketones

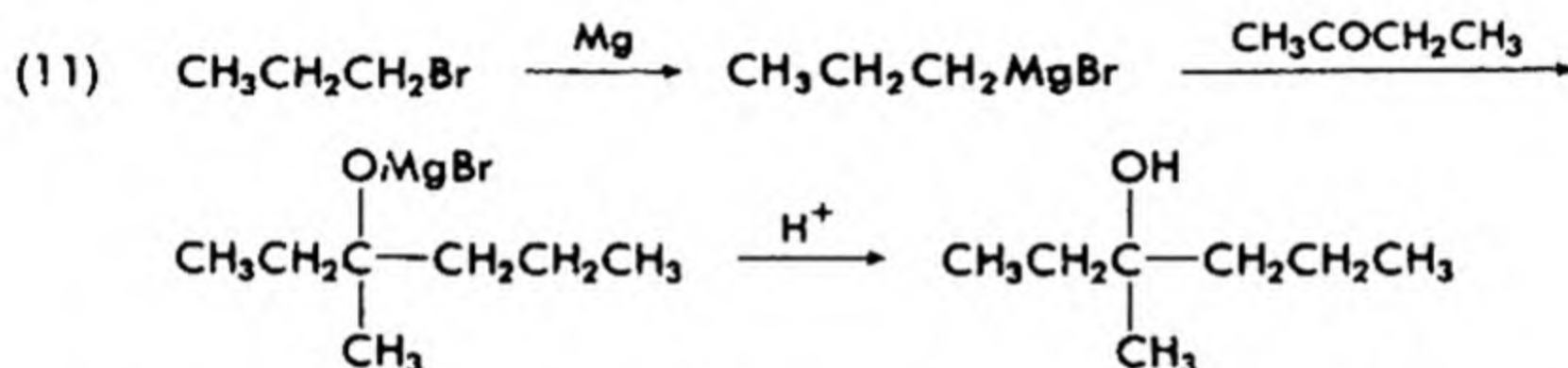
Ketones react with Grignard reagents to give salts of tertiary alcohols. All aldehydes except formaldehyde give salts of secondary alcohols. Formaldehyde gives primary alcohols having one more carbon atom than the original reagent.



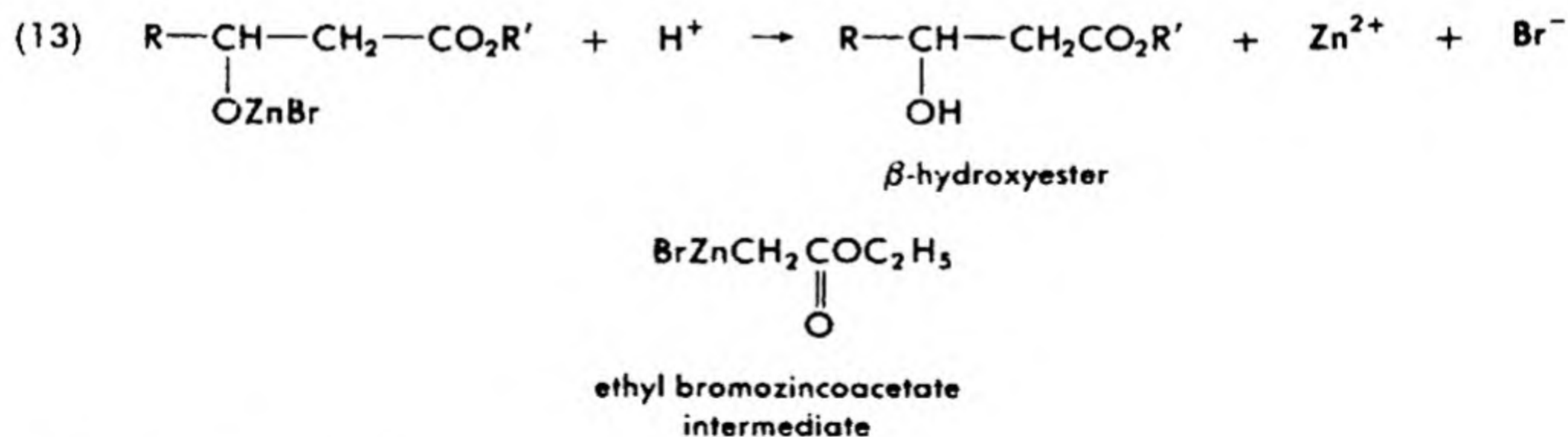
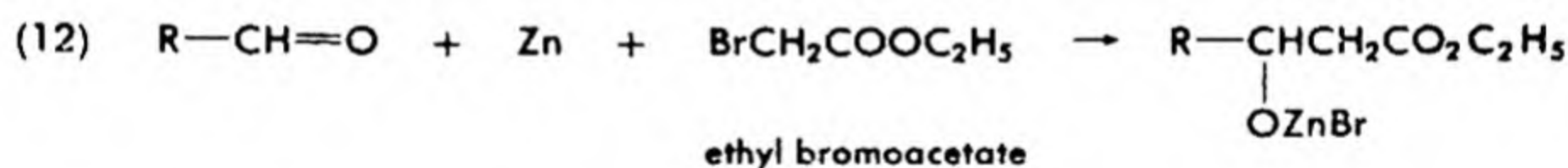
The preparation of *m*-chlorophenylmethylcarbinol in 85% yield from *m*-bromochlorobenzene is a good example of the formation of secondary alcohols as well as a clear demonstration of the formation of Grignard reagents from aryl bromides and not from aryl chlorides (§19-2B).



An example of the reaction of ketones with Grignard reagents is the formation of 3-methyl-3-hexanol.



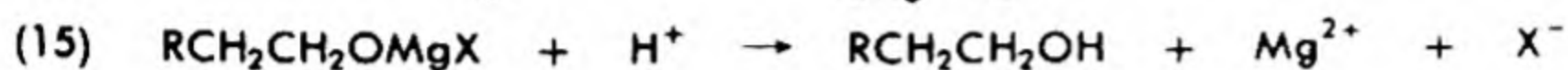
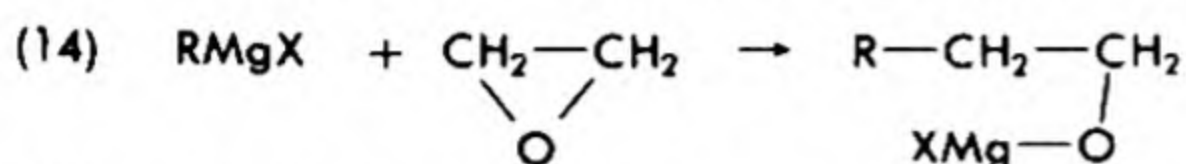
A reaction which probably involves steps like addition of a Grignard reagent to an aldehyde is the *Reformatsky reaction*. This is the synthesis of a hydroxy ester by treating an alpha-halogenated ester with zinc in the presence of an aldehyde. The intermediate organozinc compound adds to the reactive aldehyde but not to the much less reactive ester group.



C. Epoxy Compounds

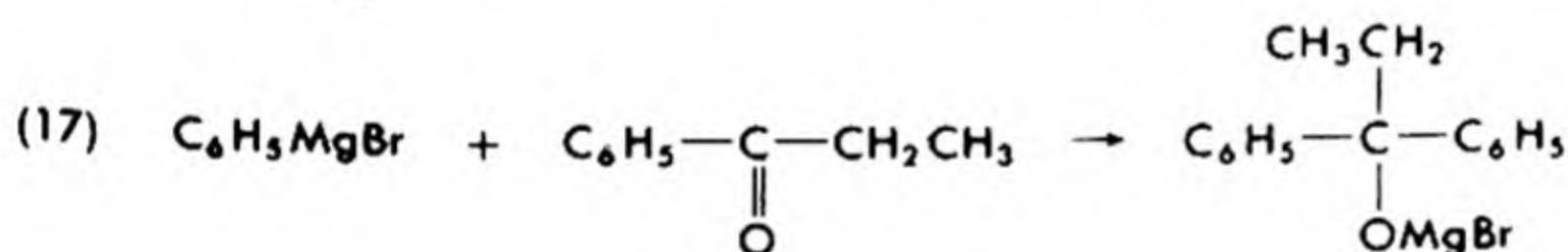
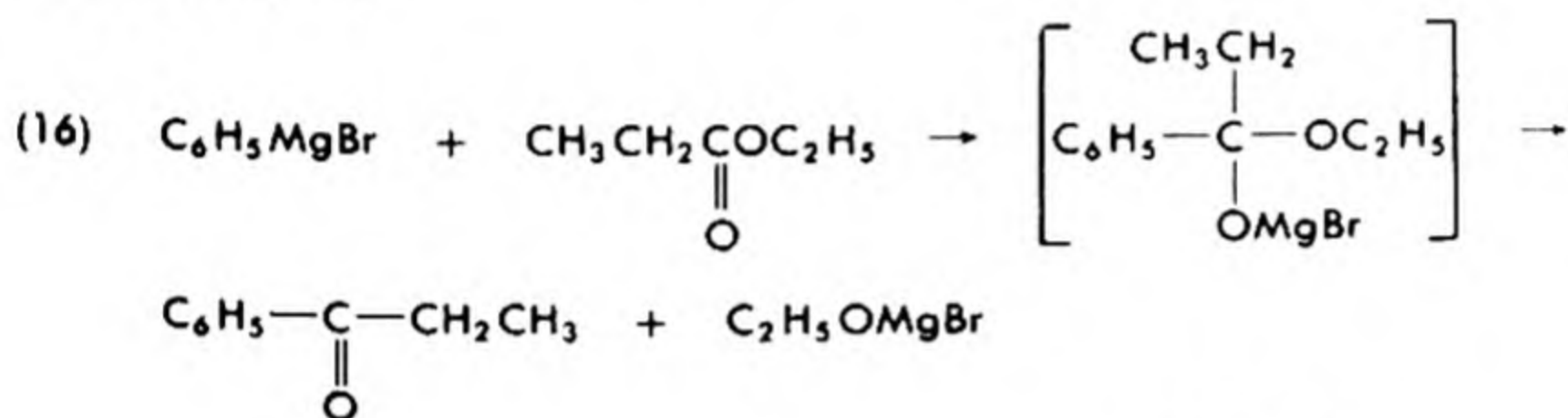
Although not polar unsaturated compounds in the usual sense of the term, epoxides, like other small ring compounds, are unsaturated in behavior. They react with Grignard reagents much like aldehydes and ketones. For example, ethylene oxide adds Grignard reagent to give a

primary alcohol in which the carbon chain has been lengthened by two carbon atoms. The yield of *n*-hexyl alcohol from *n*-butyl bromide is about 60%. However, reactions with higher epoxy compounds are often not useful as the epoxide may rearrange to an aldehyde or ketone before addition.



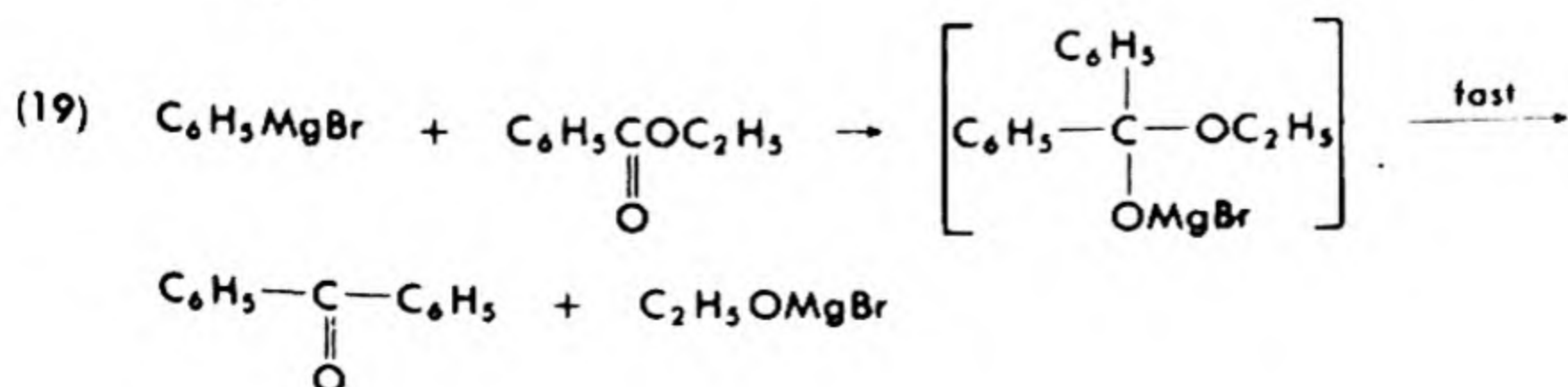
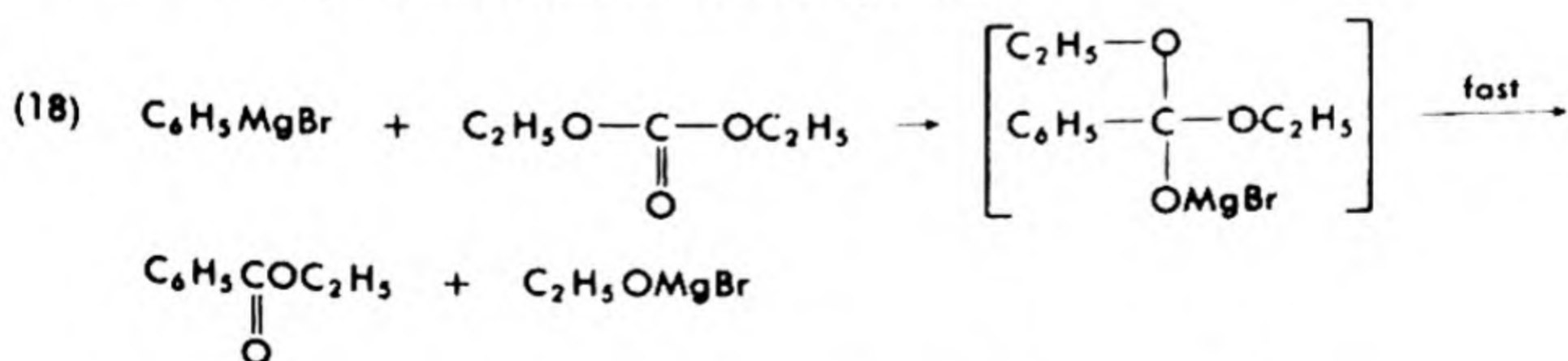
D. Acid Derivatives

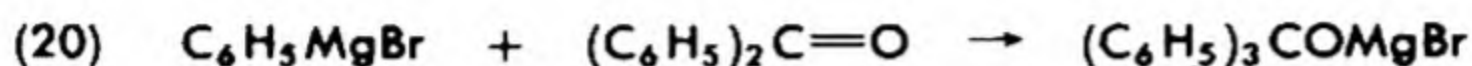
Acyl halides, acid anhydrides, and esters react with Grignard reagents to give tertiary alcohols. The initial addition complex of each of these compounds is unstable (§20-1A). The intermediate formation of a ketone from the first addition complex is the key to the formation of a tertiary alcohol (eq. 17).



Note that the reaction of an ester with a Grignard reagent gives a tertiary alcohol with at least two of the groups alike.

Carbonates can undergo this sequence twice (eqs. 18–20). The product is thus a tertiary alcohol with three like groups.

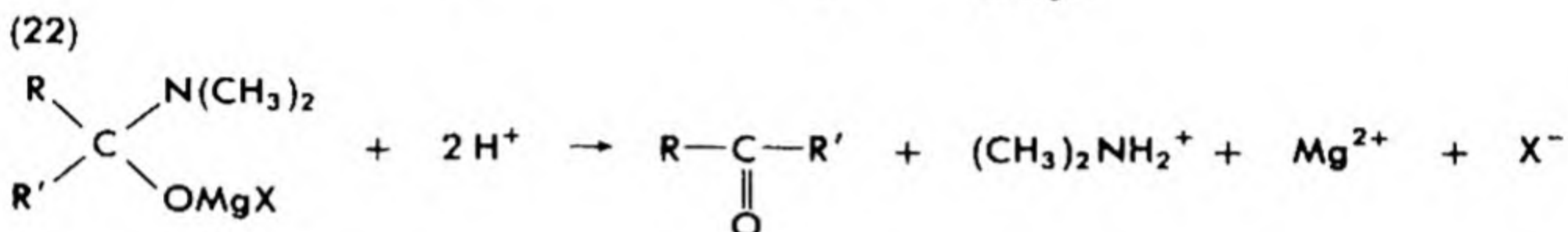
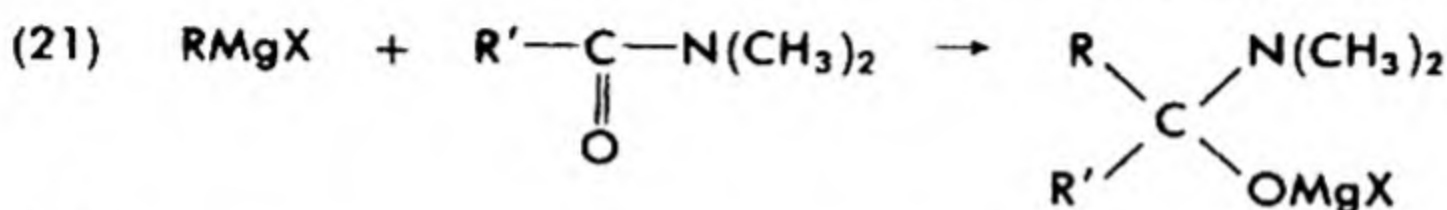




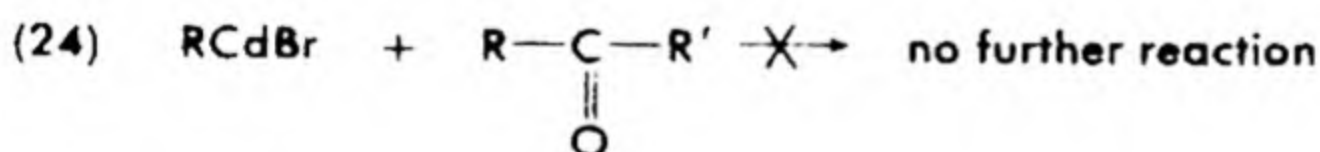
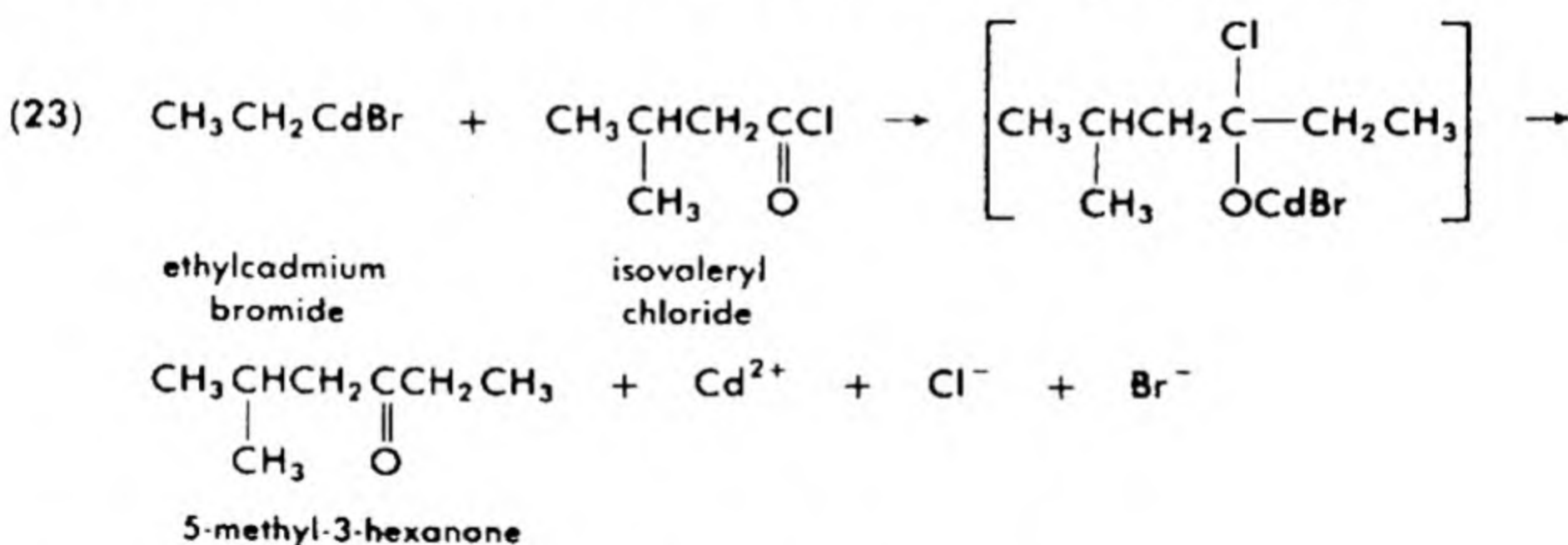
Since the second step (eq. 19) has a rate of the same order of magnitude as the first step (eq. 18), a *large excess* of the carbonate is able to compete favorably with the product ester in reaction with the Grignard reagent and thus to give a good yield of ethyl benzoate in the above example.

The reactions with chlorides and anhydrides are completely analogous, with the appropriate groups replacing $-\text{OC}_2\text{H}_5$ in the equations above.

Addition of Grignard reagent to *N,N*-dialkylamides can be used to prepare ketones, since the initial addition complex does not decompose. (Why is a simple amide not suitable?) Since the ketone is not produced until the Grignard reagent is destroyed (eq. 22), it is not further attacked.

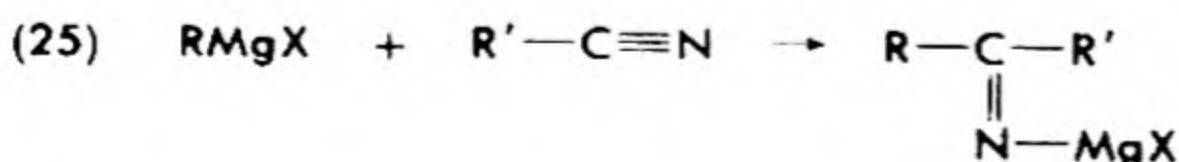


An organocadmium halide is much less reactive than a Grignard reagent. It reacts readily with acyl halides, but not with ketones. Thus, the formation of ketones with organocadmium halides does not cause tertiary alcohol formation, but provides a good ketone synthesis (eq. 23).

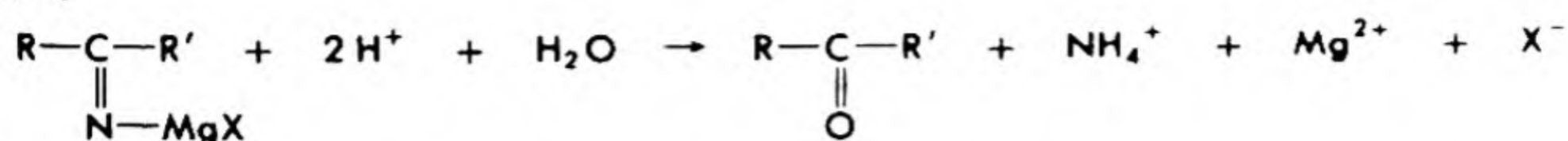


E. Nitriles

Nitriles can be used to prepare ketones more conveniently than dialkylamides.

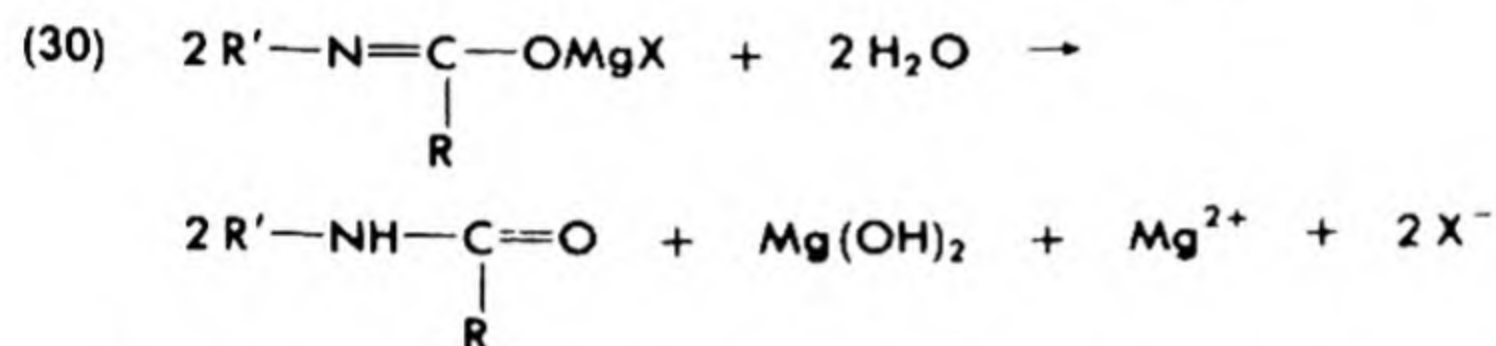
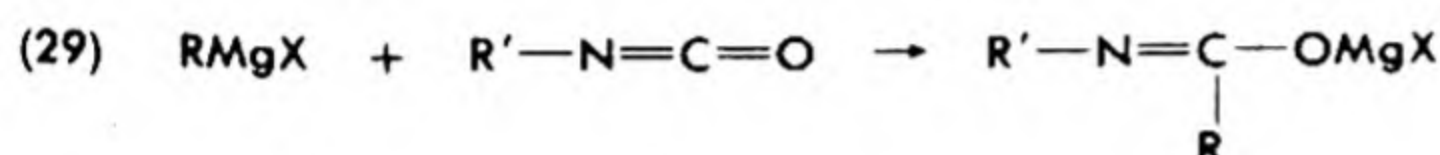
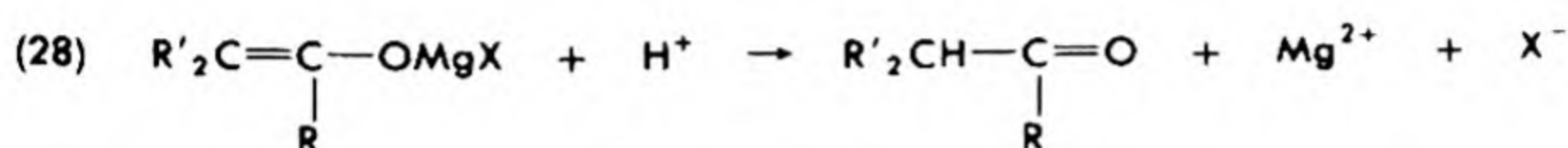
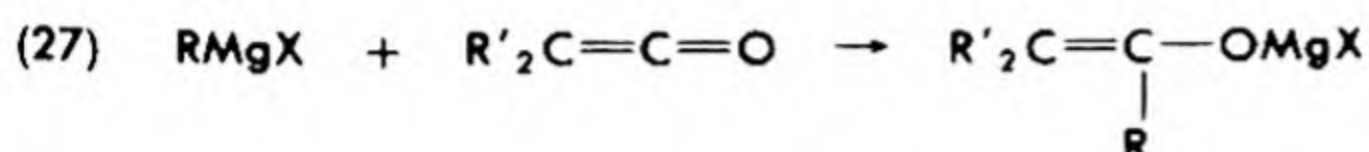


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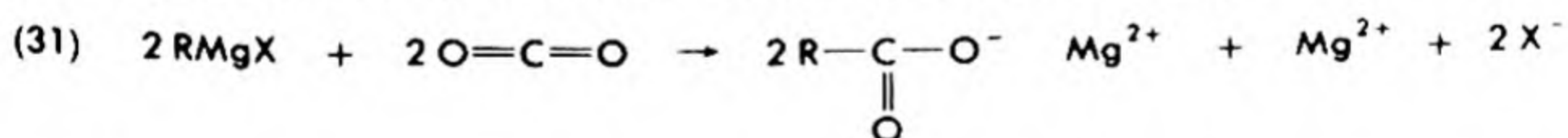
F. Cumulated Unsaturated Compounds

Grignard reagents add to the carbonyl groups of ketenes and isocyanates to give ketones and amides, respectively.



Isothiocyanates react to form thioamides.

The simpler cumulated unsaturated compounds, carbon dioxide and carbon disulfide, are also useful reagents in Grignard syntheses. These compounds add Grignard reagent to form salts of carboxylic acids and dithio acids, respectively (eq. 31). The free acids can be obtained from the salts in the usual manner. Excess of carbon dioxide or carbon di-



sulfide must be maintained. Otherwise, the Grignard reagent may add to the salts to give ketones. Carbonation of a Grignard reagent is accomplished satisfactorily by pouring the reagent onto solid carbon dioxide broken into small pieces. Besides its use as a synthetic tool, carbonation of the Grignard reagent serves to establish the position of attachment of the magnesium in the organometallic compound. Organo-lithium, organosodium, and organocalcium compounds behave similarly.

20-2 REDUCTION BY METAL HYDRIDES

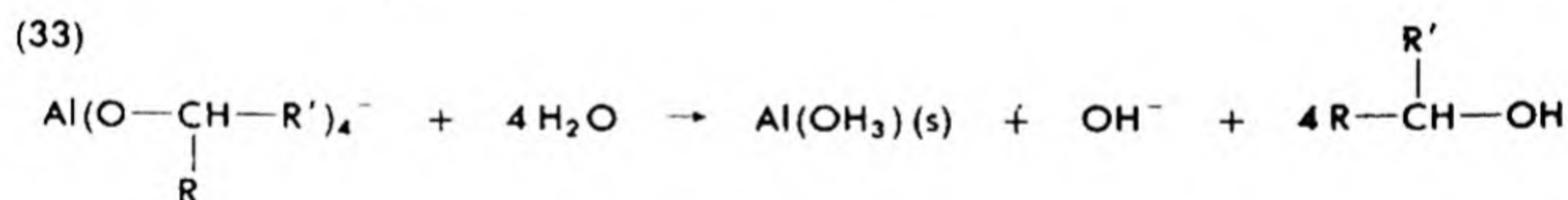
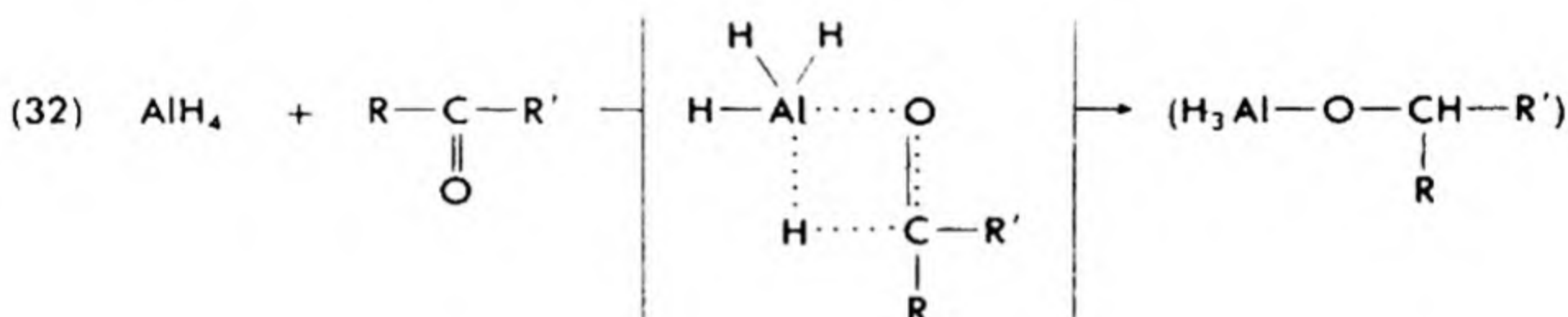
Two very useful reagents for the reduction of organic compounds with polar groups are lithium aluminum hydride and sodium borohydride. These compounds are similar in their reactions, but lithium aluminum

hydride is by far the more powerful of the two. Compounds reduced by lithium aluminum hydride are carbonyl compounds of all types, including aldehydes, ketones, esters, and carboxylic acids; epoxides, various organic sulfur compounds in higher oxidation states, nitro compounds, and halides. Sodium borohydride is more specific for carbonyl compounds, such as aldehydes, ketones, and acyl halides. Esters are reduced slowly, if at all, by sodium borohydride.

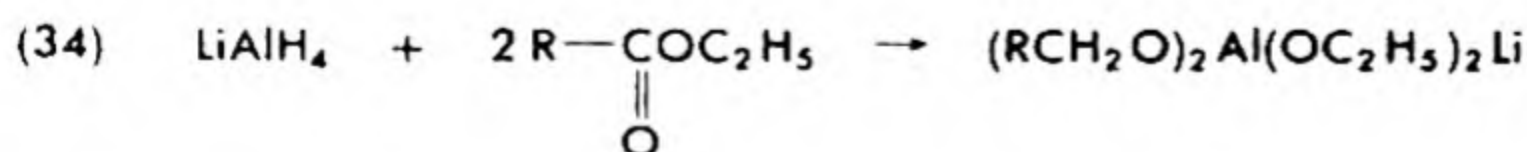
A. Types of Reactions.

The behavior of lithium aluminum hydride is considered to be analogous to that of Grignard reagents. The hydroaluminate ion performs the functions of the hydride. The following equations show the action of the hydroaluminate ion with carbonyl compounds, active hydrogen compounds, and halides.

An aldehyde displaces from one to all four of the hydrogen atoms from the hydroaluminate ion probably in the manner indicated in eq. (32). Hydrolysis of the product gives an alcohol (eq. 33).

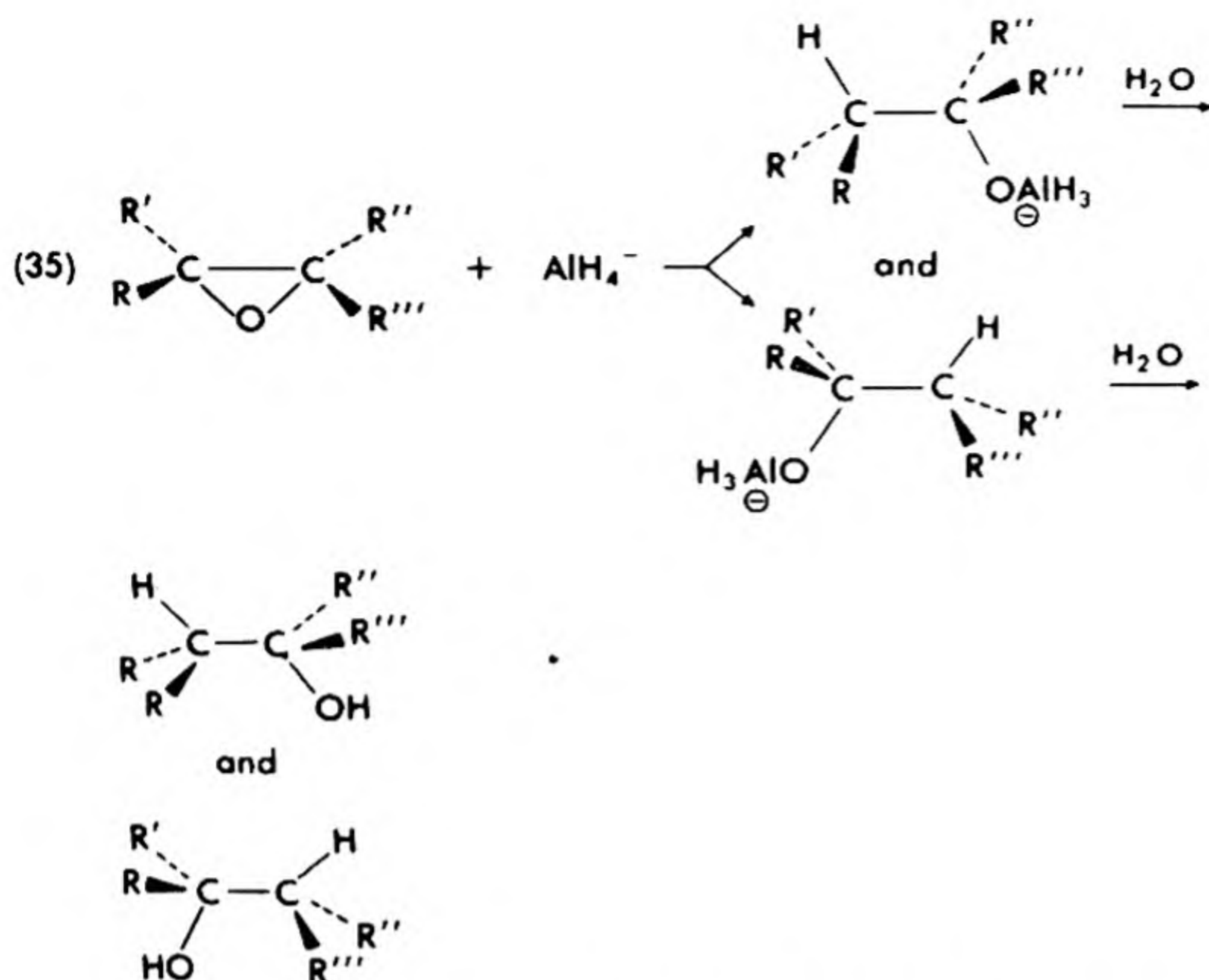


Esters and acyl halides also give alcohols. The reaction resembles that of Grignard reagents with similar compounds (§20-1).



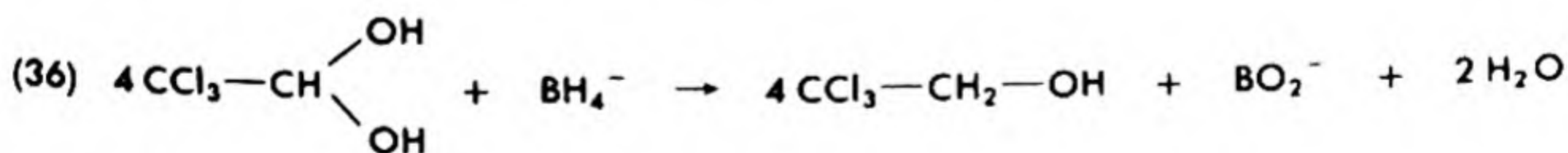
Except in unusual cases, conjugate addition (§22-1) does not occur with conjugated ene-ones and related aldehydes, esters, etc. Ordinary olefinic unsaturation is also not affected by borohydrides or aluminohydrides.

Vicinal epoxides are reduced with inversion of configuration (outline 35). This reduction cannot, therefore, occur by a four-center reaction, but may involve backside attack by one hydroaluminate ion after coordination of the oxygen atom with another.



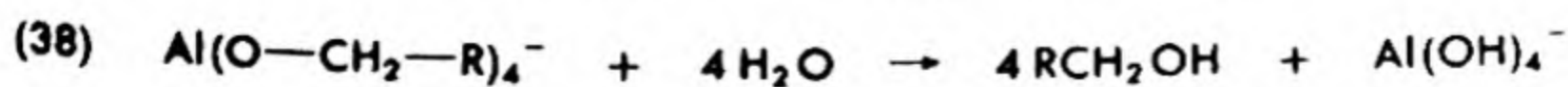
Acidic hydrogen is completely displaced in reactions with lithium aluminum hydride, even in primary amines. The reaction may not interfere with reductions, provided that enough of the reagent is used to effect reduction as well as the acid-base reaction. On the other hand, sodium borohydride is so slow in its reactions with active hydrogen that it can be utilized in cold aqueous or ethanolic solutions at pH above 6. However, stronger acids must be avoided.

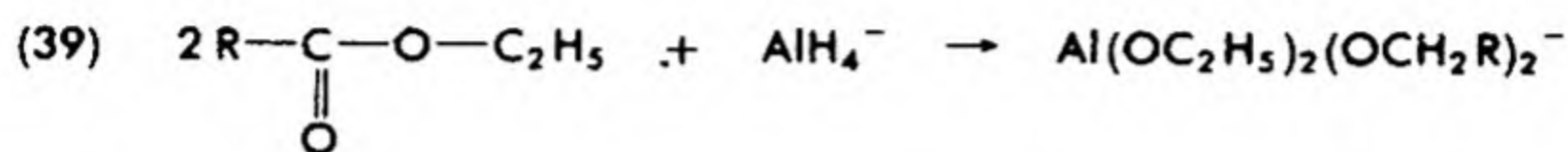
Reduction of a halide is generally much slower than the other reactions. Sodium borohydride does not ordinarily remove halogen atoms, and lithium aluminum hydride does so only after the other reactions above have occurred. This means that halogenated carbonyl compounds can be reduced to haloalcohols (eq. 36).



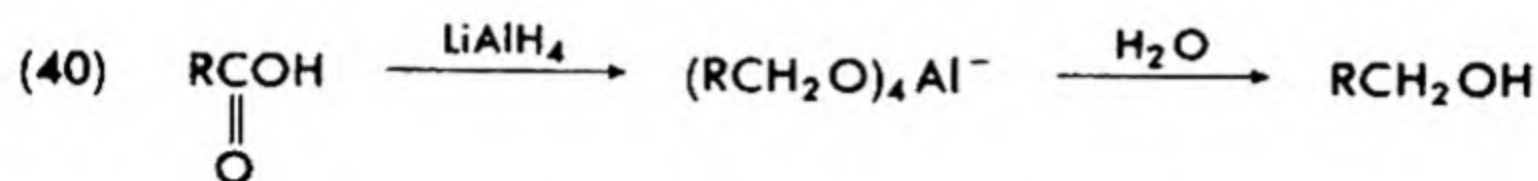
B. Typical Reductions by Hydrides

Yields of alcohols from aldehydes, ketones, esters, anhydrides, and acyl halides are uniformly high (close to quantitative).

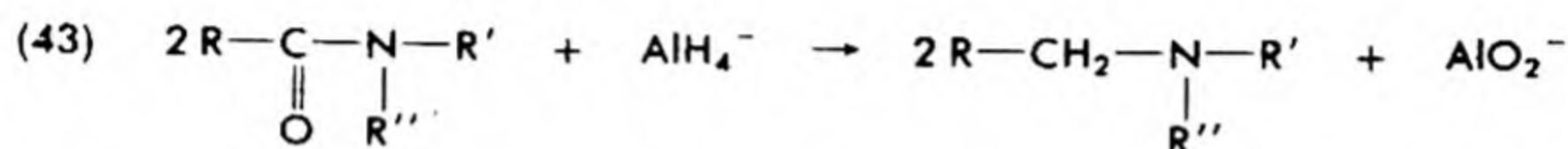
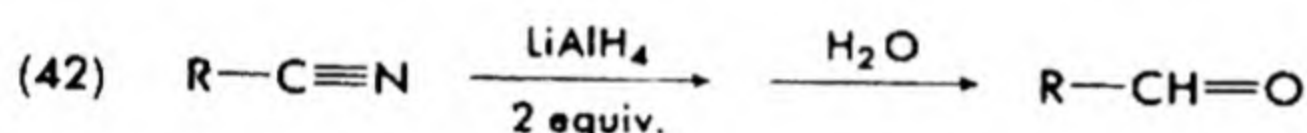
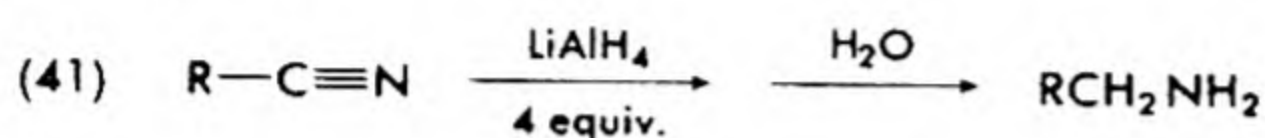




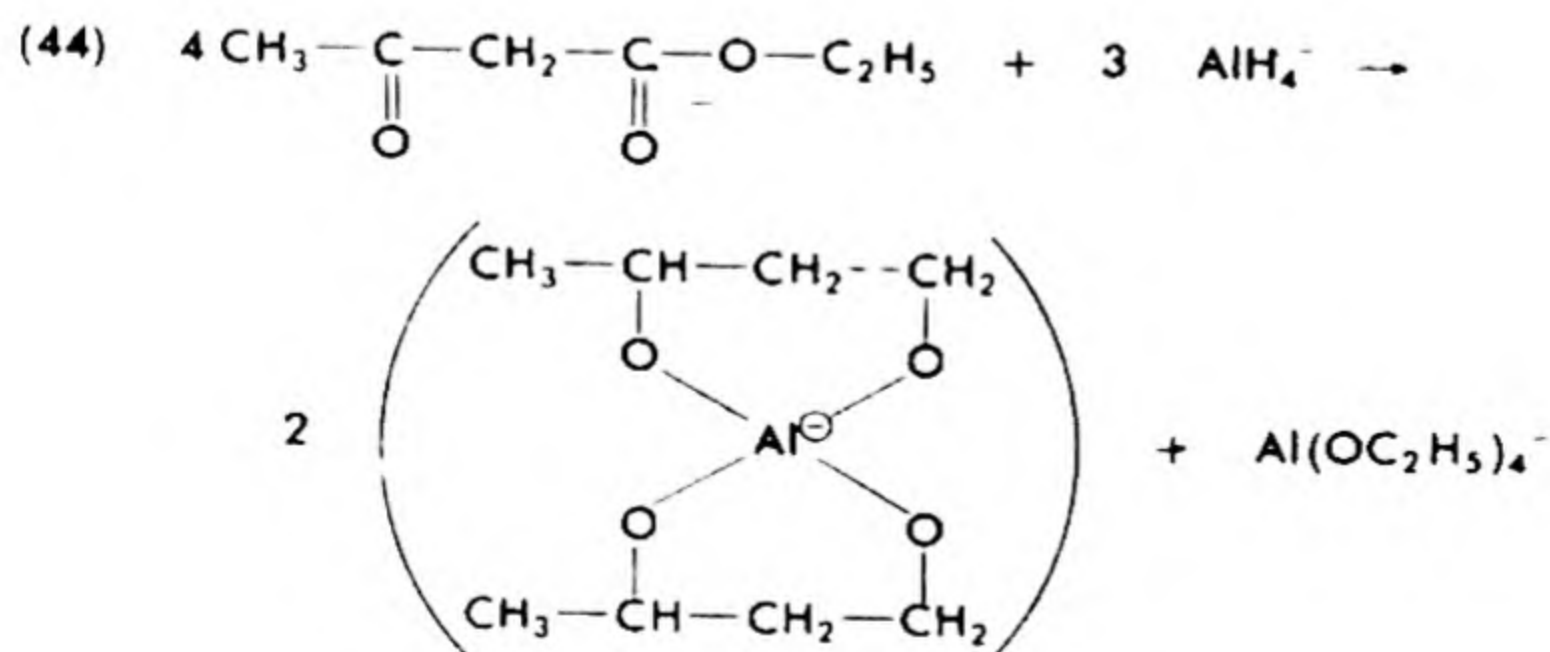
Even carboxyl groups are reduced by lithium aluminum hydride, the only reagent to accomplish this readily.

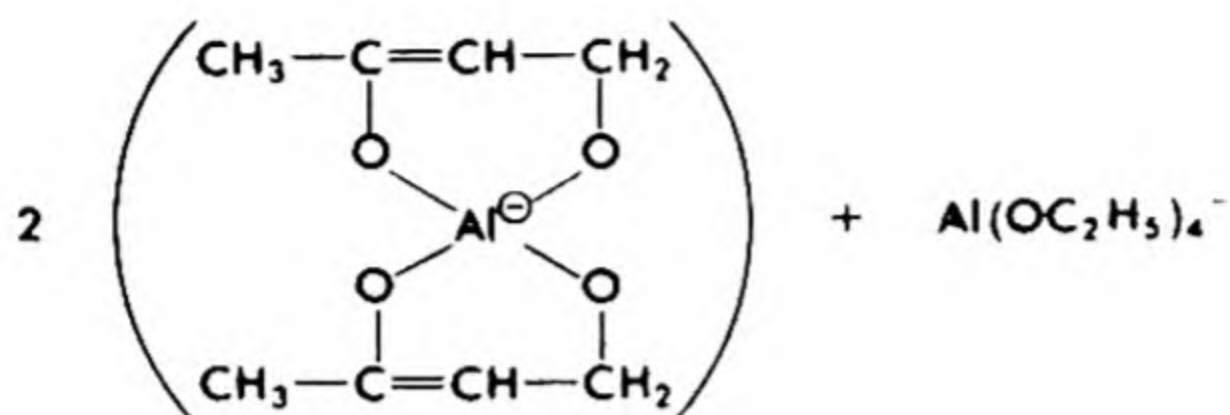
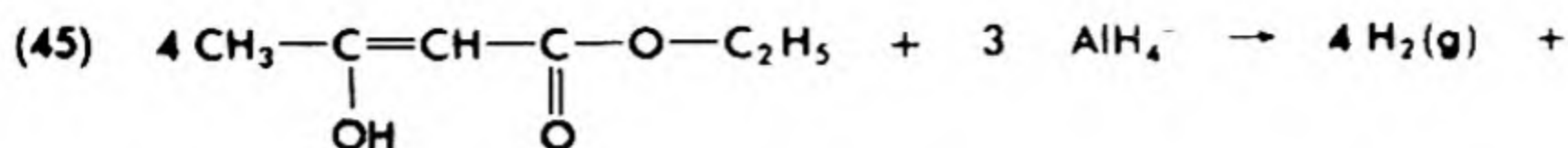


Nitriles and amides can be fully reduced to amines or partly reduced to aldehydes.



The reactions of lithium aluminum hydride with active hydrogen compounds have no significance in synthesis, since the metallated products are reconverted to the original active hydrogen compounds (or their reduction products if carbonyl or other reducible groups are present) upon hydrolysis. The reactions have been used for quantitative estimation of the amount of active hydrogen in compounds. An example is the estimation of the amount of enol form in β -keto esters. Lithium aluminum hydride reacts so rapidly with both active hydrogen and carbonyl groups that both the enol and keto forms are quickly destroyed, maintaining the equilibrium composition until all of the ester is used up. Since only the enol form produces hydrogen gas, the volume of gas obtained is directly a measure of the proportion of enol in the equilibrium mixture.

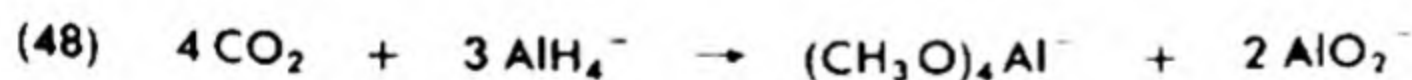
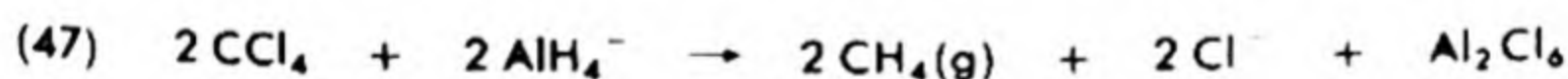




C. Handling Hazards

Metal hydrides present all of the hazards inherent in active organo-metallic compounds, including reactivity to moisture and pyrophorism, plus some of their own. Reactions with moisture, acids, and active hydrogen compounds generate hydrogen gas, always a hazardous material to handle in common equipment. Some other products of such action are strong alkalis, hence dusts from metal hydrides must not be inhaled. Lithium ions are poisonous. So also are boron hydrides (boranes) produced by the action of strong acids on sodium borohydride.

Fires, so readily started by metal hydrides, are very difficult to extinguish. Water, carbon tetrachloride, and even carbon dioxide merely provide more fuel for the fire, since all three react vigorously with lithium aluminum hydride and, at combustion temperatures, with sodium borohydride.



An effective extinguisher is powdered limestone.

SUPPLEMENTARY READINGS

- Brown, W. G., "Reductions by Lithium Aluminum Hydride," *Org. Reactions*, **6**, 469-509 (1951).
 Gaylord, N. G., *Reduction with Complex Metal Hydrides*, Interscience, New York, 1956.
 Kharasch, M., and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice Hall, Englewood Cliffs, N. J., 1954.
 Shriner, R. L., "The Reformatsky Reaction," *Org. Reactions*, **1**, 1-37 (1942).

QUESTIONS AND PROBLEMS

1. Explain why lithium aluminum hydride is a more powerful reducing agent than sodium borohydride. Base the explanation on the atomic structure and charge distribution in boron and aluminum compounds.

2. Write equations for the reactions that occur between the reagents in the mixtures listed below.

- | | |
|--|--|
| a. 2°-butylmagnesium bromide and ethyl formate | c. acetaldehyde, zinc, and ethyl α -bromovalerate |
| b. phenylcadmium bromide and ethyl formate | d. ethylmagnesium iodide and carbon disulfide |

3. Write equations for the reactions of lithium aluminum hydride and sodium borohydride with the following compounds. Give structural formulas for organic compounds.

- | | |
|---------------------------------|--------------------|
| a. methyl 3°-butyl ketone | d. aldol |
| b. benzalacetophenone | e. methyl pivalate |
| c. <i>m</i> -chlorobenzaldehyde | |

4. Show how the following compounds can be prepared from *n*-propyl alcohol and suitable inorganic and organic reagents by the Grignard method.

- | | |
|----------------------------|--|
| a. <i>n</i> -butyl alcohol | d. methyl <i>n</i> -propyl ketone |
| b. 2-pentanol | e. ethyl di- <i>n</i> -propyl carbinol |
| c. butyric acid | f. butyrophenone |

5. Complete the following outlines, writing the structural formulas for compounds required and the formulas of organic intermediates and products.

- a. phenylmagnesium bromide + (?) \rightarrow (?) $\xrightarrow{\text{HCl}}$ benzophenone
- b. isopropylmagnesium bromide + (?) \rightarrow (?) $\xrightarrow{\text{HCl}}$ isopropyl phenyl ketone
- c. *n*-butylmagnesium bromide + (?) \rightarrow (?) $\xrightarrow{\text{H}_2\text{O}}$ *N*- α -naphthylvaleramide
- d. methylmagnesium iodide + (?) \rightarrow (?) $\xrightarrow{(?)} \rightarrow$ (?) $\xrightarrow{\text{HCl}}$ propynoic acid
- e. ethylmagnesium iodide + (?) \rightarrow (?) $\xrightarrow{\text{HCl}}$ 3,5-heptanedione

6. Show how the following compounds can be prepared from ethanol and methanol as the only organic starting materials. Indicate essential inorganic reagents and conditions. Use structural formulas of organic compounds.

- | | |
|----------------------------|----------------------------|
| a. 2°-butyl bromide | e. diisopropyl ether |
| b. <i>n</i> -butyl alcohol | f. 3°-butylamine |
| c. 3°-butyl alcohol | g. 2-hydroxypropanoic acid |
| d. 2-hydroxybutanoic acid | h. 3-amino-3-ethylpentane |

7. Show how the desired compounds can be prepared either from the suggested raw materials or by adding the suggested increments to the molecule. Indicate reagents and essential conditions. Use structural formulas of organic compounds.

- | | |
|---|---|
| a. benzoic acid from benzene | g. triphenylcarbinol by adding a phenyl group twice |
| b. dimethyl- <i>n</i> -propylcarbinol from acetone | h. ethyl cyclohexanecarboxylate by adding the ethoxycarbonyl group |
| c. methyl vinyl ketone from ketene and acetylene | i. 2- ¹⁴ C-acetonitrile from sodium ¹⁴ C-carbonate |
| d. ethyl 3°-butyl ketone from isobutylene and propionitrile | j. 1- ¹⁴ C-ethanol from methanol and sodium ¹⁴ C-carbonate |
| e. 2-phenylethanol by adding two carbon atoms | k. <i>N,N</i> -di- ² H-isopropylamine from acetone and deuterium oxide |
| f. 1-phenylethanol by adding two carbon atoms | |

21

Reactions of "Active Hydrogen" Compounds. Enols and Enolates as Intermediates

21-1 GENERAL CONSIDERATIONS

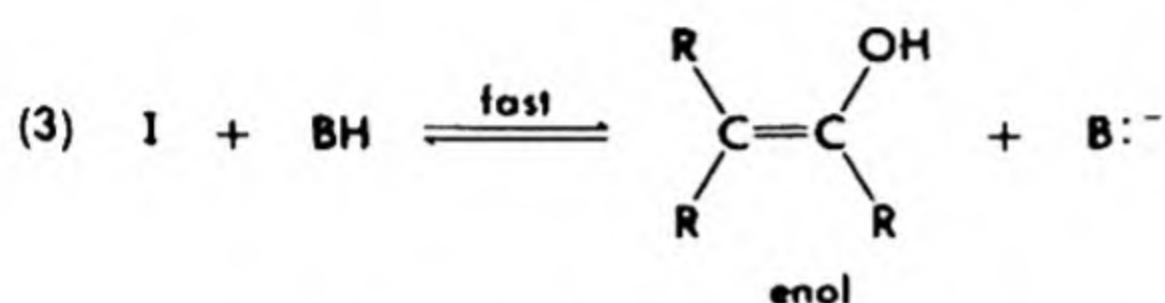
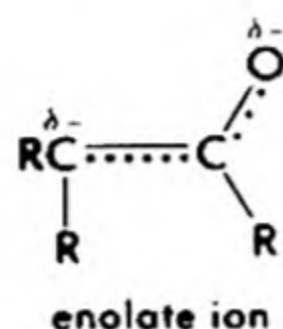
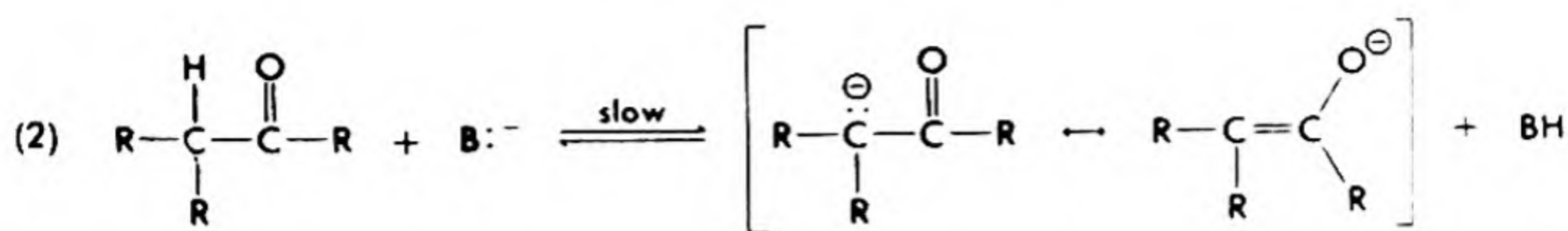
Hydrogen atoms which are alpha to polar unsaturated π bonds are acidic (see §10-2D) because of resonance stabilization of their conjugate bases. Many reactions of such compounds proceed through their conjugate bases, or enolate ions. These include base-catalyzed or base-promoted halogenations, deuterium exchange, condensations, alkylations, racemizations (§31-9A), among others, of aldehydes, ketones, esters, nitriles, and primary and secondary nitro compounds as well as of certain aromatic compounds. Acids catalyze the transformation of these compounds to their enol forms, which are intermediates in the analogous acid-catalyzed reactions.

21-2 KETO-ENOL AND ANALOGOUS TRANSFORMATIONS

The transformation of an aldehyde or ketone to its enol (eq. 1) and the reverse reaction are catalyzed by both acids and bases. In general, the

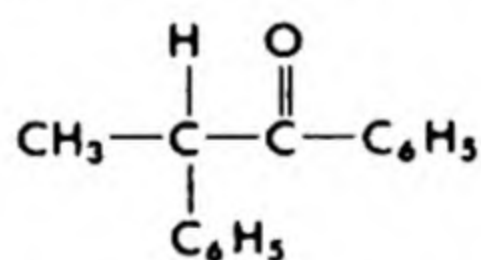


keto form is the more stable, and with simple aldehydes and ketones the enol form is present only in microscopic amounts. With more complex systems the enol form reaches easily measurable quantities and in certain cases even predominates. The mechanism for base-catalyzed enol formation involves first the removal of a proton from the α carbon atom (eq. 2) to give resonance-stabilized enolate ion, which then, in the absence of other reagents with which the enolate might react more rapidly, accepts a proton on the oxygen atom (eq. 3).



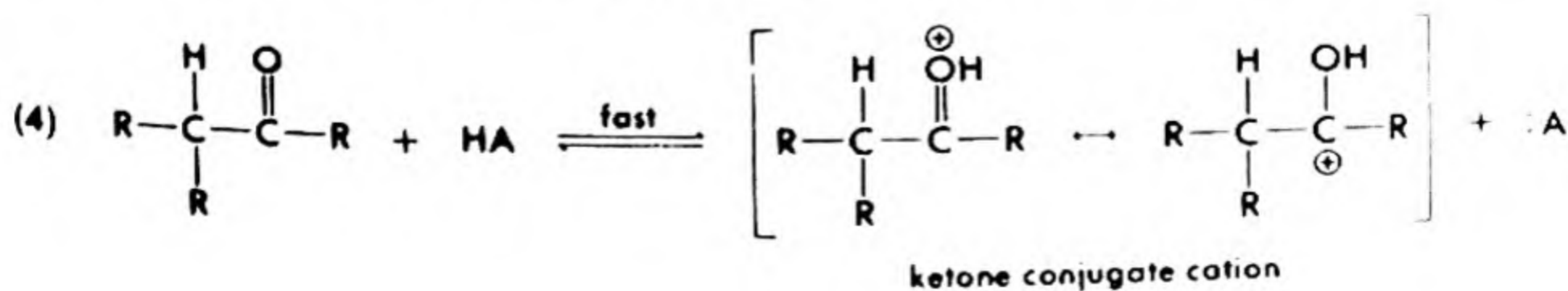
As all of these reactions are reversible, it should be clear that this process predicts that there will be hydrogen exchange with the solvent (if BH is the solvent). This can be observed by conducting the reaction in a solvent which is deuterium- or tritium-labeled. As both the enolate ion and the

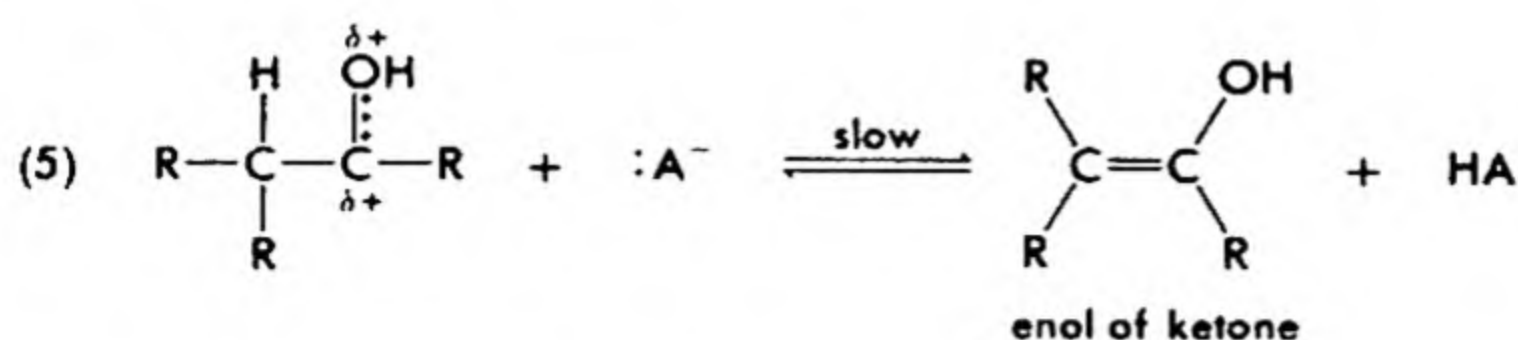
enol are planar at the >C=C<O^- portion of the system, a ketone which is optically active at the α -carbon atom, such as



will undergo base-catalyzed racemization readily. One notes that this reaction should have the same rate as that for deuterium exchange, as both reactions have eq. (2) as the rate-determining step.

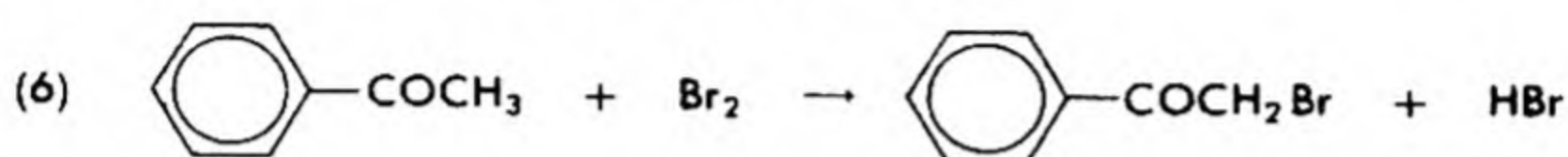
Acid-catalyzed enol formation proceeds as shown in eqs. (4) and (5). Again, the reversibility of the reaction and the fact that eq. (5) represents the rate-determining step explain the observation that deuterium exchange and loss of activity in suitable systems proceed at similar rates.



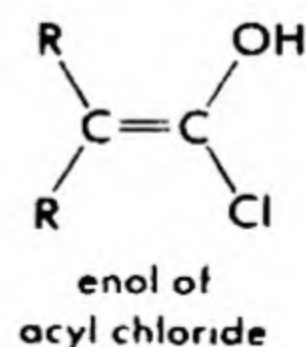
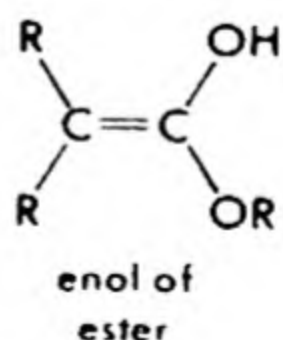
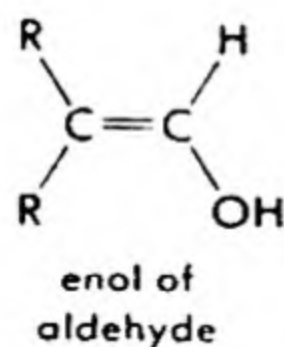
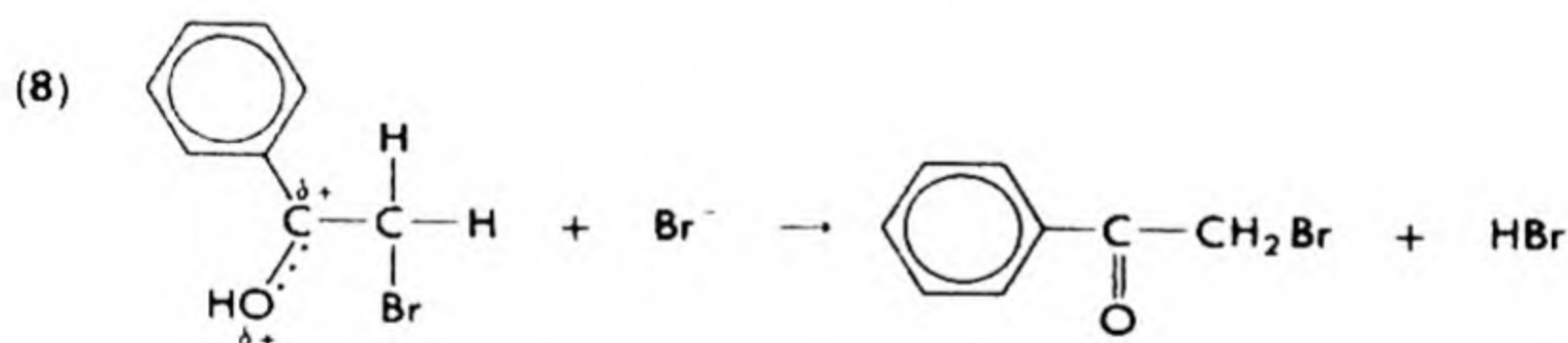
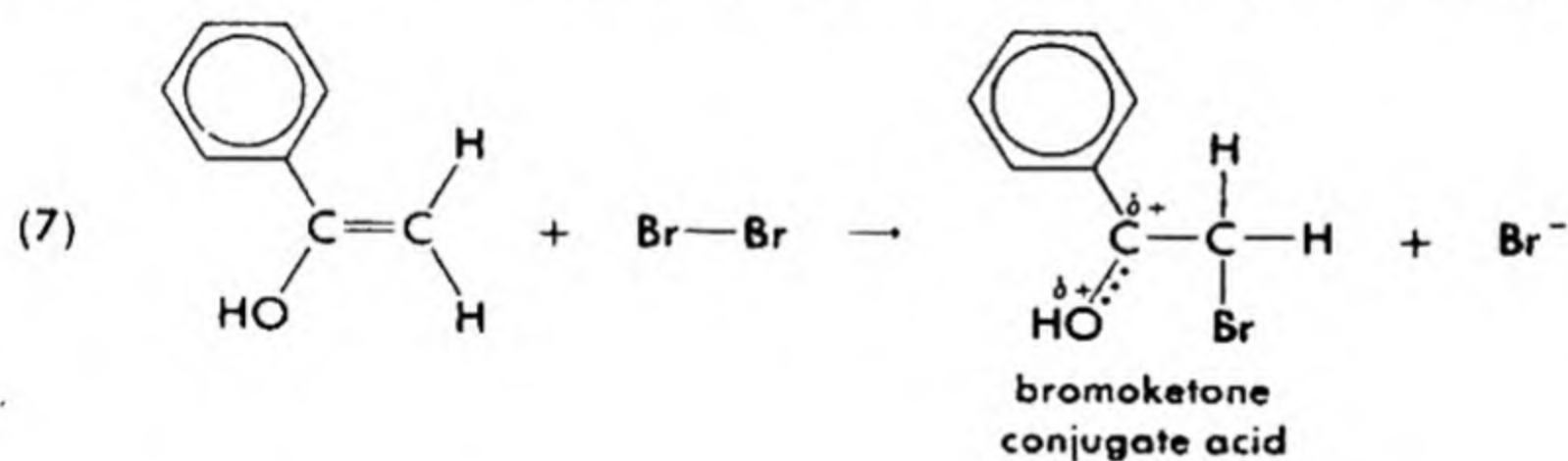


A. Acid-Catalyzed Halogenation

When an aldehyde or ketone is treated with chlorine or bromine, halogenation results. An example is given in eq. (6). It is observed that the reaction is catalyzed by acids. As the product hydrogen halide is a strong acid, the reaction is autocatalytic.

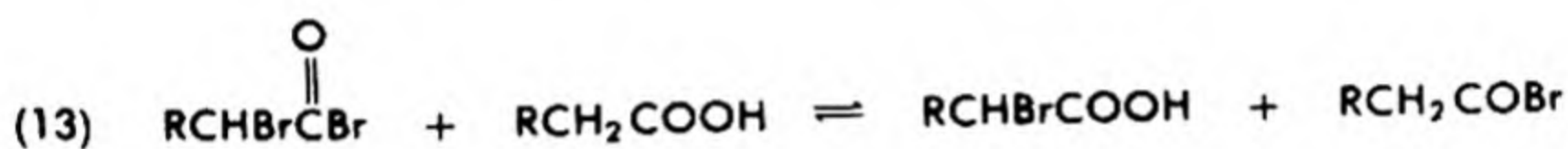
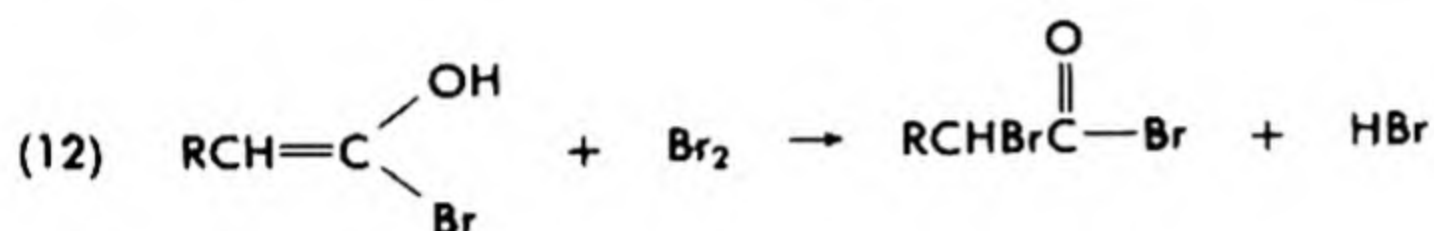
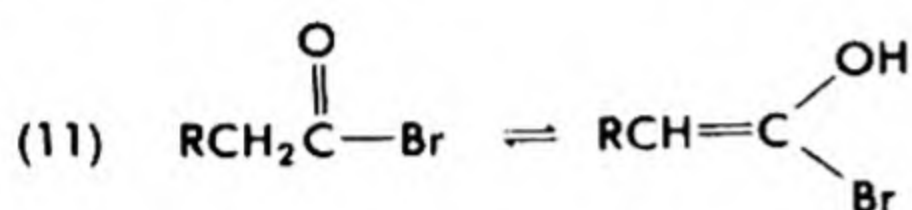
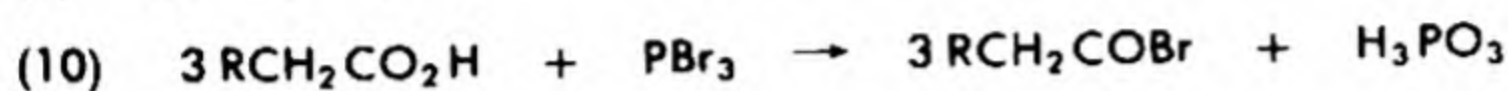
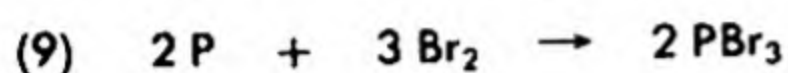


The function of the acid is to convert the carbonyl compound to the enol (eqs. 4 and 5), which is then halogenated by a variation of the standard olefin reaction with halogens. Donation of a positive halogen species to the double bond (eq. 7) is followed by a proton loss from the conjugated acid of the bromoketone to give bromoacetophenone (eq. 8). Enols of

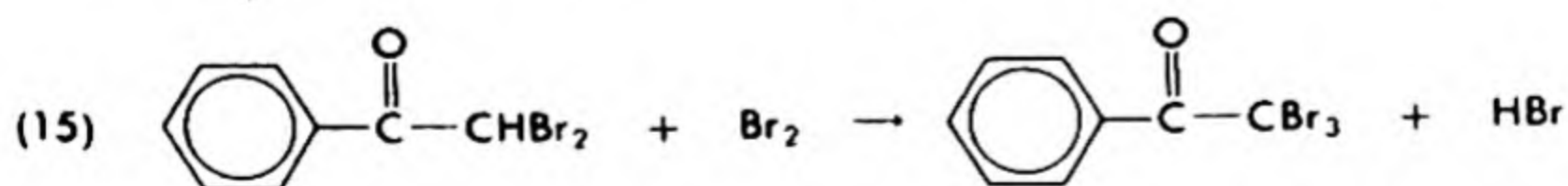
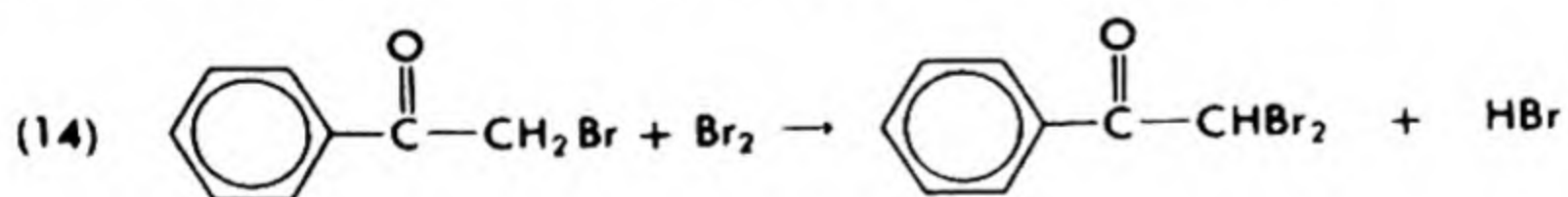


aldehydes, esters, and acid chlorides can all be halogenated. The latter and the bromine analogue are the intermediates in the Hell-Volhard-Zelinsky reaction.

The *Hell-Volhard-Zelinsky reaction* is an extremely useful synthetic procedure for the preparation of α -chloro and α -bromo acids. It involves treatment of acids with halogen and a small amount of red phosphorus, and probably involves the following steps. An α -halo acid halide can be obtained if equivalent phosphorus is used, or exchange with acid may occur (eq. 13) if only catalytic amounts of phosphorus are used.

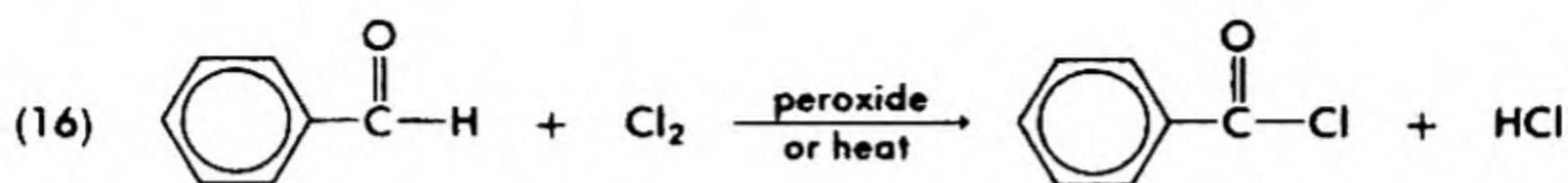


As the halo-carbonyl compound is a weaker base (due to inductive effect of halogen compared with hydrogen) than the corresponding carbonyl compound, the equilibrium represented in eq. (4) is much less favorable for it than for the original ketone (or other carbonyl compound). The result of this is that it is more difficult to put in the second halogen than the first one and still harder to replace a third hydrogen. This has the important result that one can therefore control the chlorination or bromination of these compounds to give monohaloketones, dihaloketones or trihaloketones in good yield by adding precisely the stoichiometric amount of halogen (eqs. 6, 14, and 15).



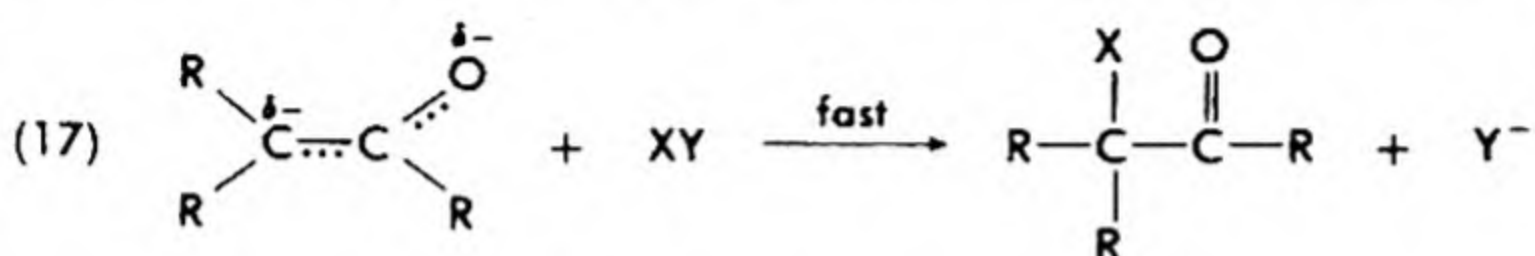
Only α -hydrogens are replaced by acid-catalyzed halogenation, as only these are involved in enol formation. If no α -hydrogens are present, these reactions do not occur. Of course, other functional groups may react by other mechanisms. For example, benzaldehyde is inert to the acid-catalyzed chlorination, but readily undergoes free-radical chlorina-

tion (see §15-3) to give benzoyl chloride. This is an industrial preparation (eq. 16).



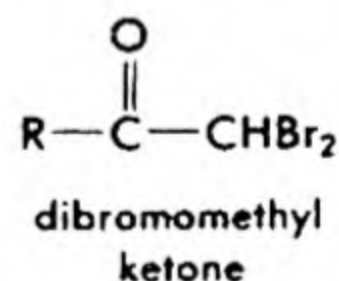
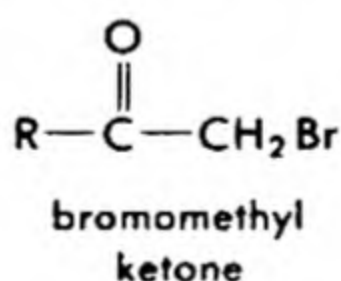
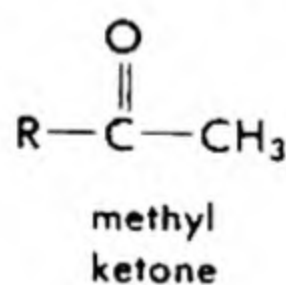
B. Base-Catalyzed Halogenations

Base-catalyzed halogenations occur through the intervention of the enolate ion (eq. 2), followed by reaction of the ion with halogen or halogen donor (eq. 17). This is known because the rates of iodination,



bromination, and chlorination of a given ketone are all identical, independent of halogen donor concentration, and identical with deuterium-exchange rates in the absence of halogen. This is because the slow step in all of these reactions is the formation of enolate ion.

In base-promoted halogenation the second halogen is substituted faster than the first and the third faster than the second, whenever there is more than one alpha hydrogen available on the same carbon. The acid strengths of the three ketones, methyl, bromomethyl, and dibromomethyl, increase in that order due to the electron-attracting ability of halogen compared with hydrogen and, as might be anticipated, their rates of removal by bases also increase in that order. For this reason it is not

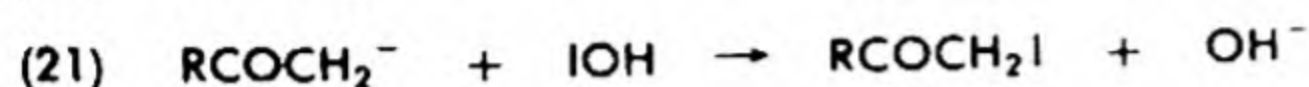
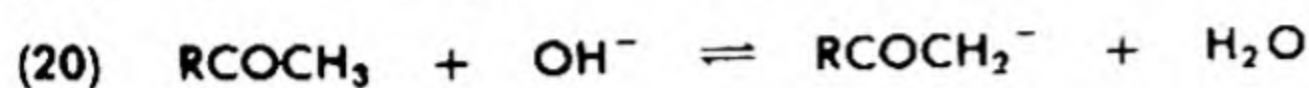
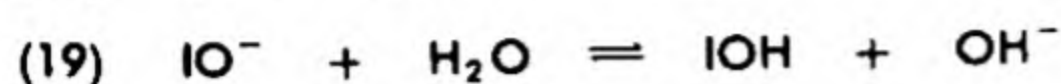
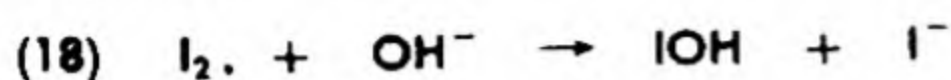


ordinarily possible to replace less than all of the active hydrogen atoms on a given α -carbon atom by a base-catalyzed reaction.

21-3 THE HALOFORM REACTION

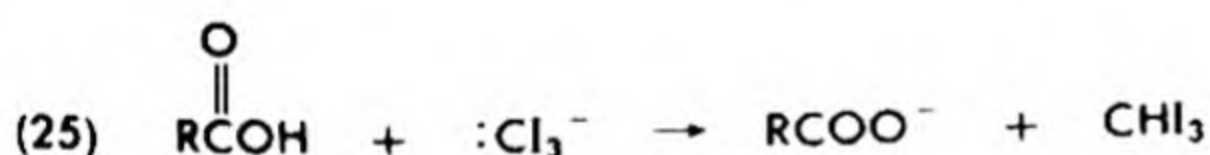
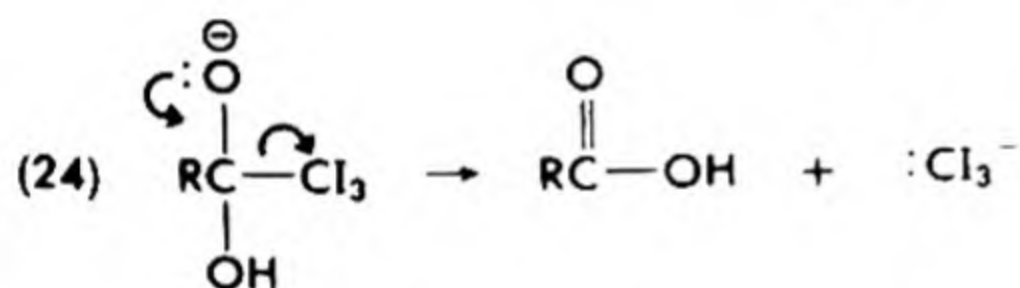
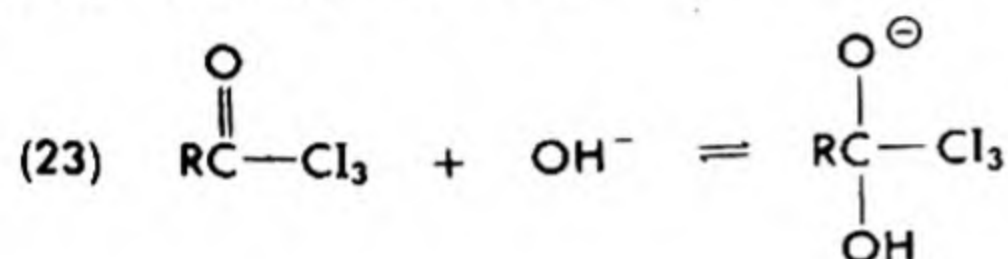
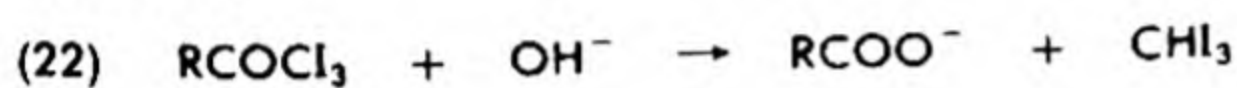
The ready reaction of methylcarbonyl compounds with halogens in the presence of bases to form trihalomethylcarbonyl compounds is used in the haloform reaction. Here the reagent is ordinarily prepared by dissolving the halogen in sodium hydroxide solution (eq. 18), thus obtaining a solution of sodium hypohalite, NaOX, at a pH low enough that some hypohalous acid is present in equilibrium with hypohalite ion. The halogena

tion then follows the course:

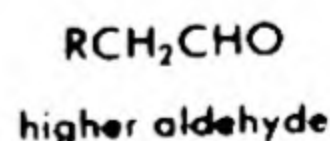
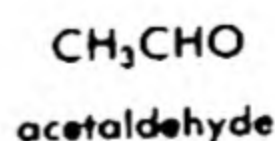
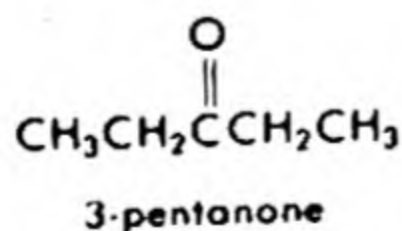
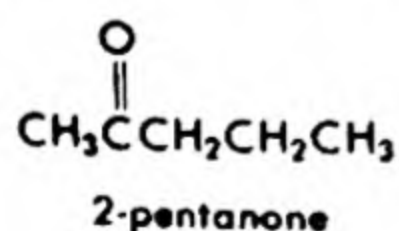


repeat to RCOCl_2

Trihaloketones are readily cleaved by alkali to haloform and salts of carboxylic acids (eq. 22). This reaction has a mechanism precisely analogous to that involved in ester hydrolysis (see §17-2) and represented by eqs. (23), (24), and (25). The overall reaction is called the *haloform reaction*.

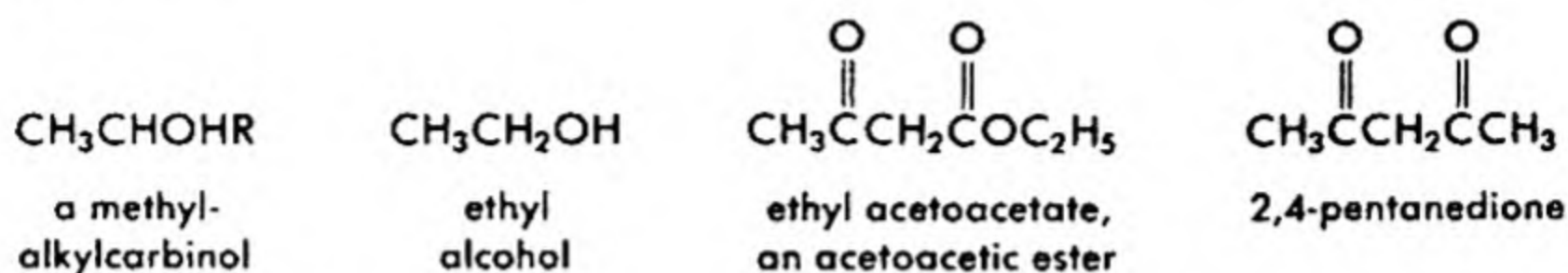


The haloform reaction finds two principal uses. For analytical purposes it is used to distinguish methyl ketones from other ketones, as other ketones have at most two α hydrogen atoms on a given carbon atom and therefore cannot give the haloform. Compare 2-pentanone with 3-pentanone. Acetaldehyde is the only simple aldehyde giving the haloform reaction. Compare formulas below. For qualitative tests, sodium hypoiodite is used rather than hypochlorite or hypobromite as iodoform is a water-insoluble solid with a characteristic melting point and odor and is therefore readily identified.



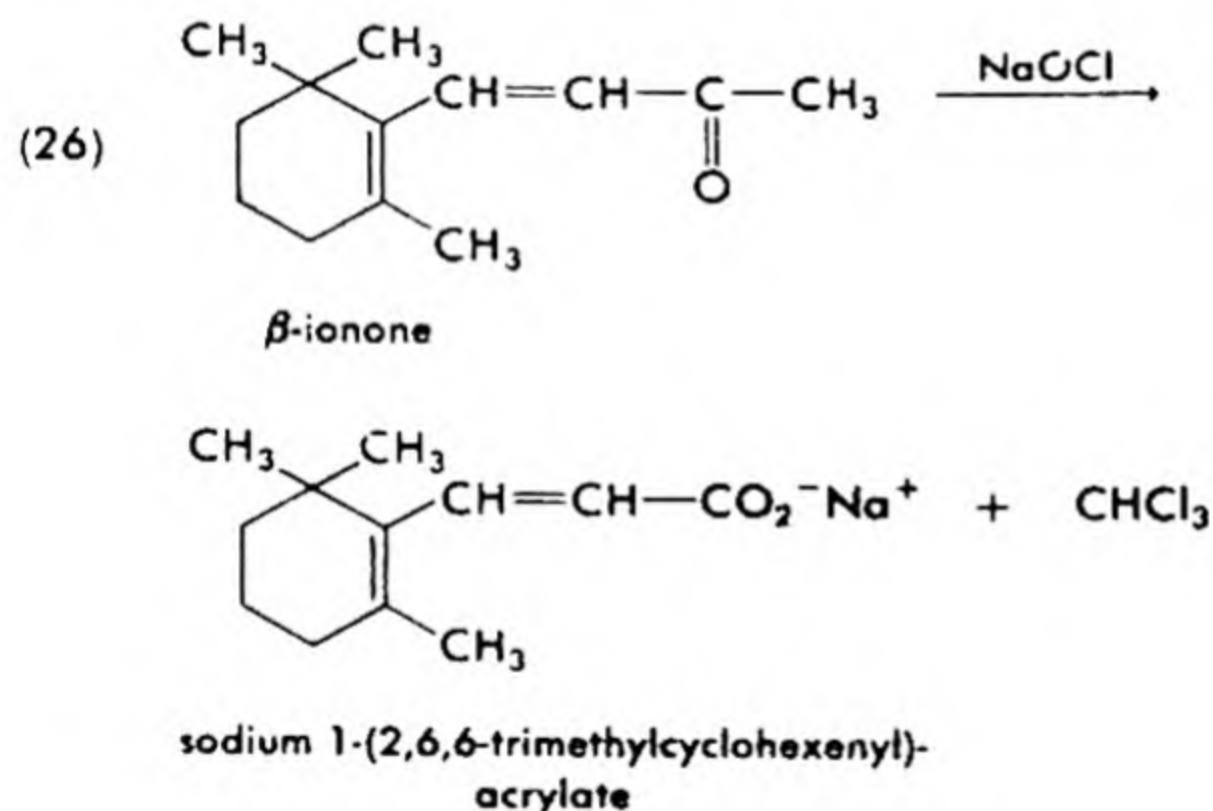
Primary and secondary alcohols are readily oxidized by hypohalite solutions and so methylalkylcarbinols and ethyl alcohol give positive

iodoform reactions. When a compound contains hydrogens more acidic than those of a methylcarbonyl function, halogenation occurs at this position and the iodoform test fails. Examples are acetoacetic esters and 2,4-pentanedione, where the methylene group α to both carbonyl groups is halogenated.



As a tool in synthesis it is the resulting acid, not the haloform, that is the object of the reaction. Here hypochlorite or hypobromite is used. Yields of acids range from 40% to nearly 100%. Halogenation of methylene groups on the side of the carbonyl group opposite to the methyl group accounts for most of the yield loss of acid from aliphatic ketones.

Many oxidizable groups, including multiple bonds, are not affected by the hypohalite, so that this is especially useful for the conversion of methyl alkenyl ketones to the unsaturated acids.

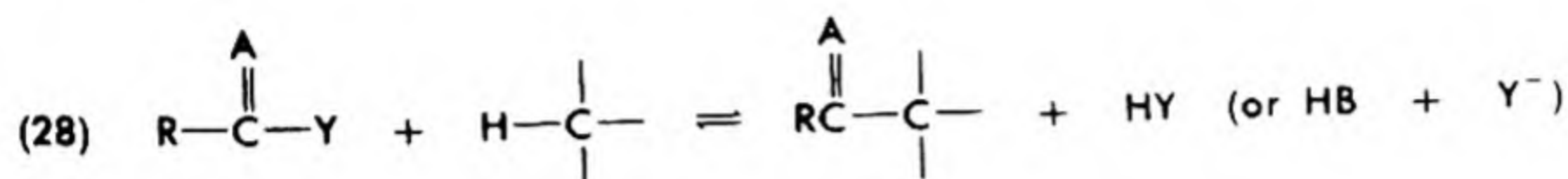
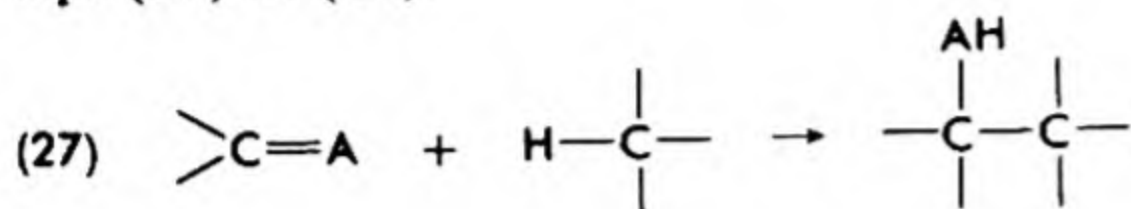


21-4 CONDENSATIONS

The term condensation has been associated with two different reaction types in organic chemistry, not to mention the physical process. In one, a condensation is a reaction in which two organic molecules combine, then split out some small inorganic unit, such as water. In this sense, esterification and replacements of carbonyl oxygen are condensations. The second usage of the term applies to those reactions in which two organic compounds or 2 moles of one compound join together, forming a new carbon-to-carbon bond. In a limited sense, the term condensation applies only to those reactions in which one molecule containing a reactive carbon-to-

hydrogen bond adds to another molecule having a polar unsaturated group in such a way that a carbon-to-carbon bond is formed.

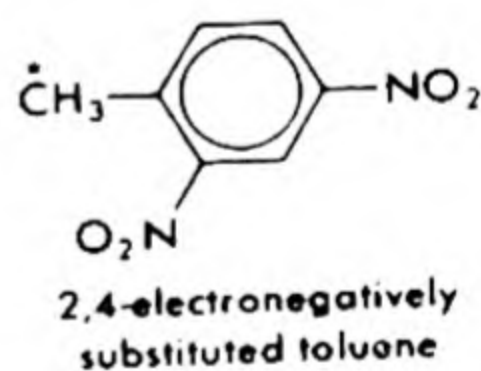
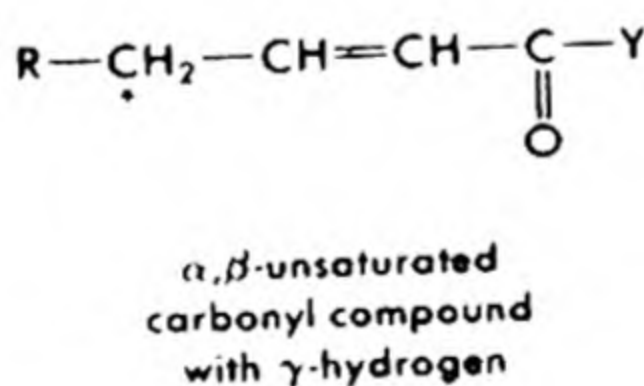
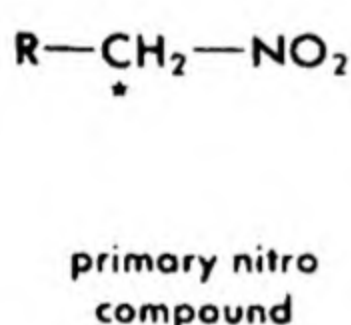
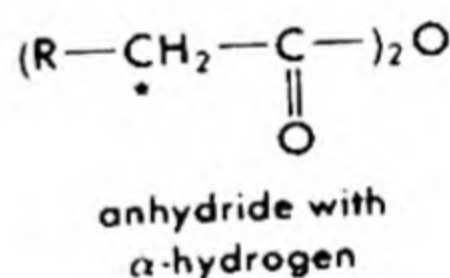
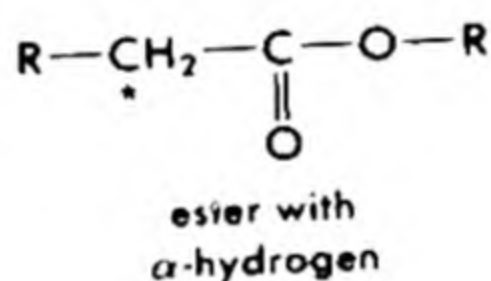
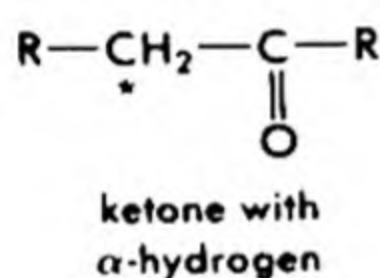
The overall reaction for the latter type of condensations is given as eqs. (27) or (28).



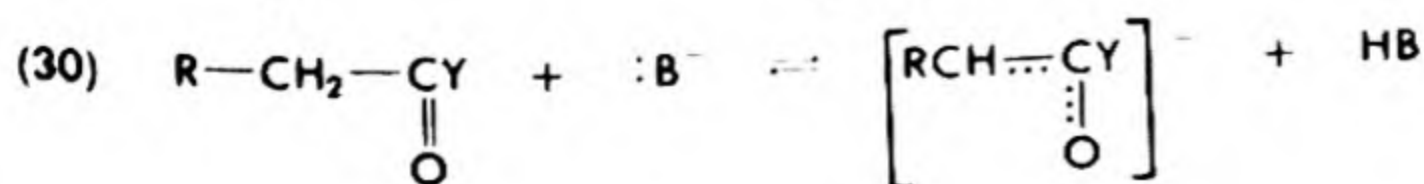
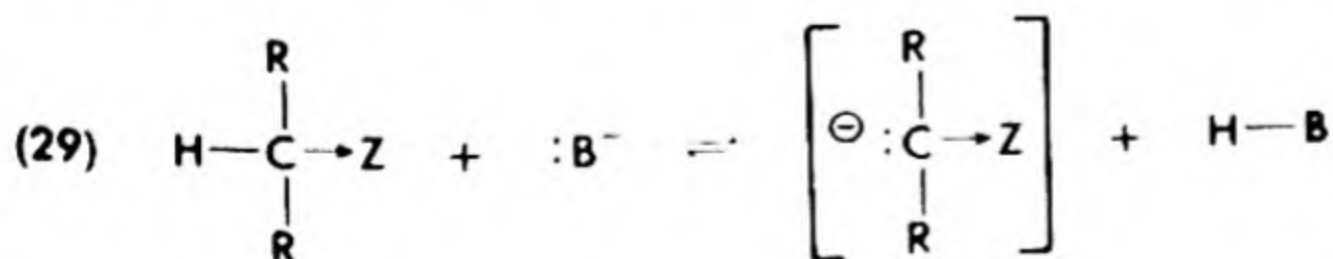
A. Reactants

The electrophile is a compound with a polar unsaturated bond, usually carbonyl or cyano. Aldehydes, ketones, and acid derivatives such as esters are examples.

The nucleophile is formed from a compound with an active hydrogen atom on a carbon atom. Some typical active carbon-hydrogen bonds are indicated by asterisks in the formulas below. Each has an electron-attracting group (Z in eq. 29) which stabilizes a negative charge on the conjugate anion.



The active hydrogen compound itself is usually not nucleophilic, but is transformed into a nucleophile by a basic catalyst (eq. 29). For carbonyl compounds, enolate-ion formation is involved (eq. 30).

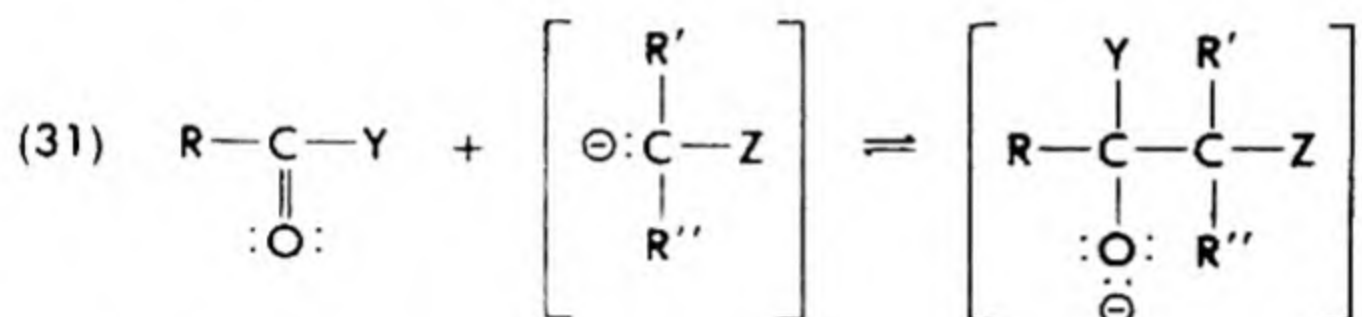


Ring-activated compounds can act as nucleophiles.

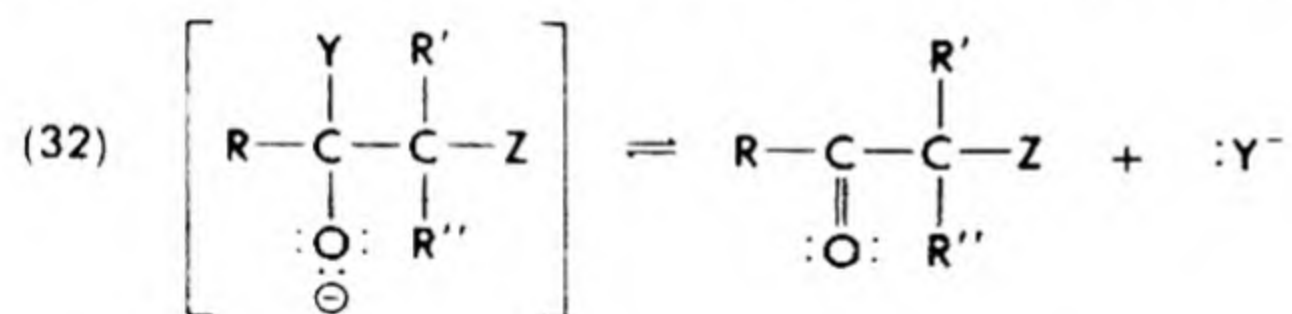


B. Specific Reaction Mechanisms

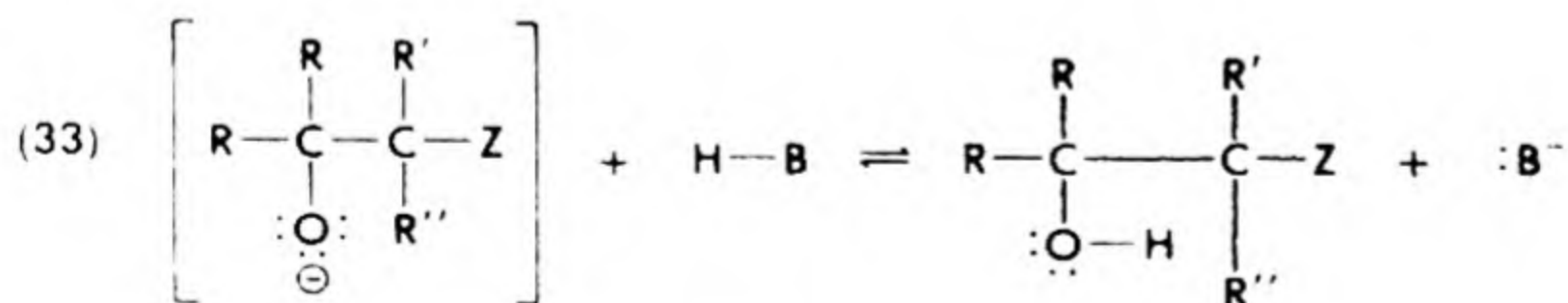
The negative carbon atom in the intermediate at the right of the equilibrium (eq. 29) is a very powerful nucleophile. Even if present in hardly detectable amounts, it attacks the positive center of a carbonyl or like group so that a condensation occurs (eq. 31).



What happens to the addition product depends on the nature of R and Y. If Y can form a stable anionic group, it usually does so (eq. 32).



If this cannot occur, the basic oxygen atom may take a hydrogen ion away from a solvent molecule or another molecule of active hydrogen compound (eq. 33).



That these are not the only fates awaiting condensed molecular fragments will become apparent enough after a few examples are given.

C. Typical Condensations

Because condensation reactions are so often referred to by the names of their discoverers, one needs to learn to associate each type of condensation with its name.

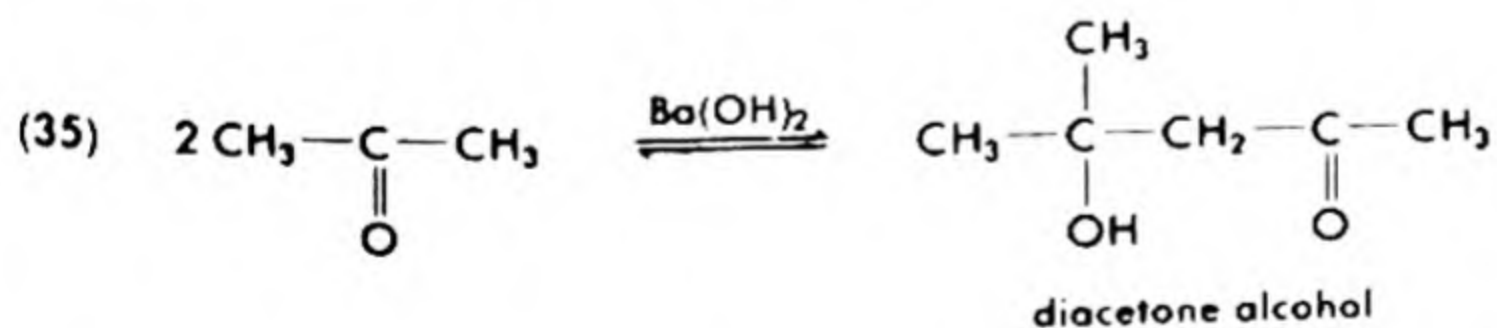
(1) *Aldol Condensations.* The aldol condensation is a condensation between 2 moles of aldehyde or ketone in the presence of a base to give a β -hydroxycarbonyl compound. Aldehydes have the more reactive carbonyl groups, hence undergo the condensation more readily than ketones. In fact, they undergo condensation so readily that they tend to polymerize in the presence of bases. Consequently, poor yields of products are often obtained along with considerable tar.

The name aldol originates from the name given to the condensation product from acetaldehyde.

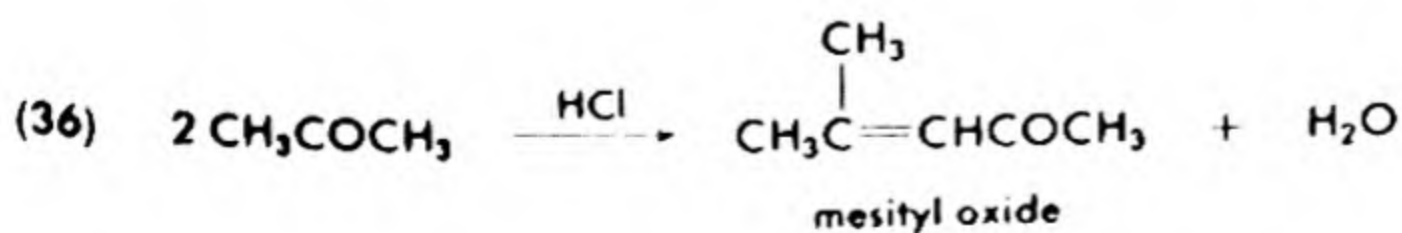


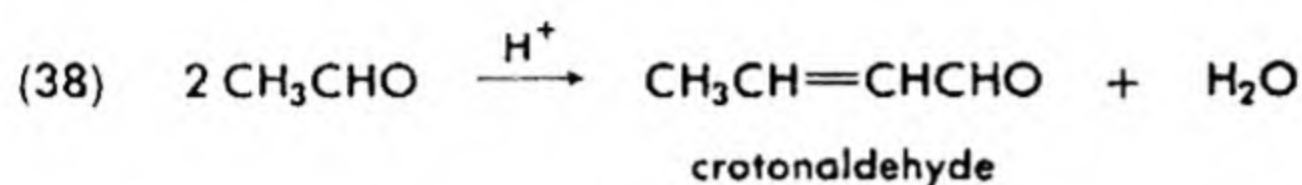
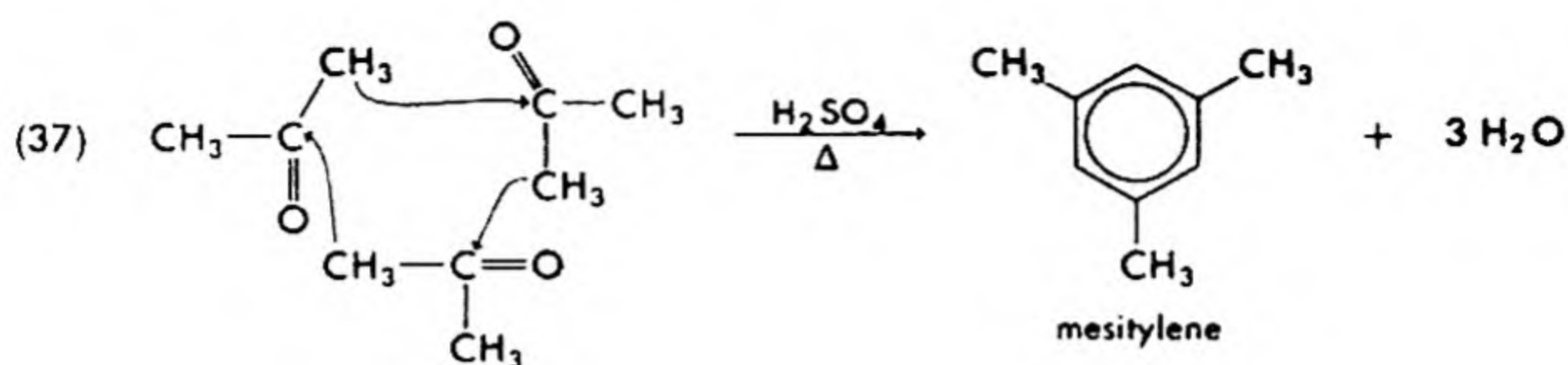
Steric factors operating in this reaction (note that the trigonal atom became tetrahedral) make the equilibrium point for ketones unfavorable to condensation. Hence, special methods are necessary to induce ketones to condense satisfactorily. In a reaction between an aldehyde and a ketone, the ketone furnishes the active methylene group, the aldehyde the carbonyl function.

The method used to condense a ketone is illustrated by the preparation of diacetone alcohol, obtained in 71% yield using barium hydroxide in a Soxhlet extraction thimble to catalyze the conversion out of contact with the mass of product. Since the acetone is volatile, whereas the product is not, the small portion of diacetone alcohol that forms as the reaction progresses runs into the boiler, and remains there, while the recovered acetone distills up again to contact the catalyst.

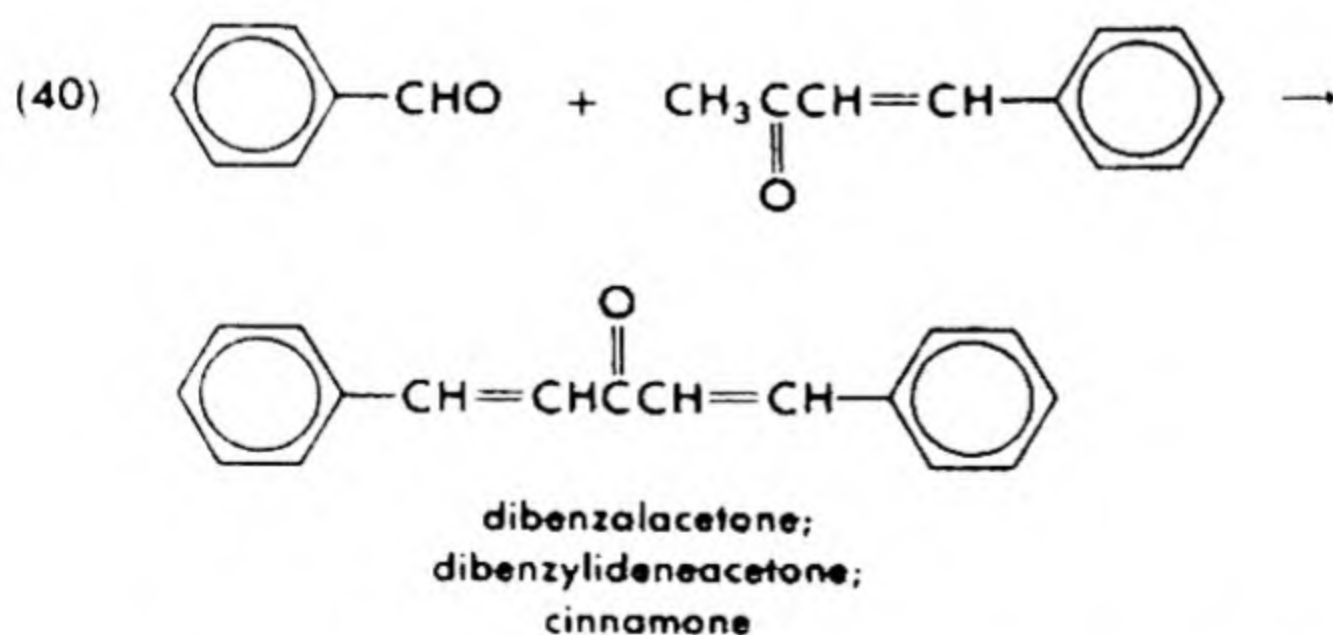
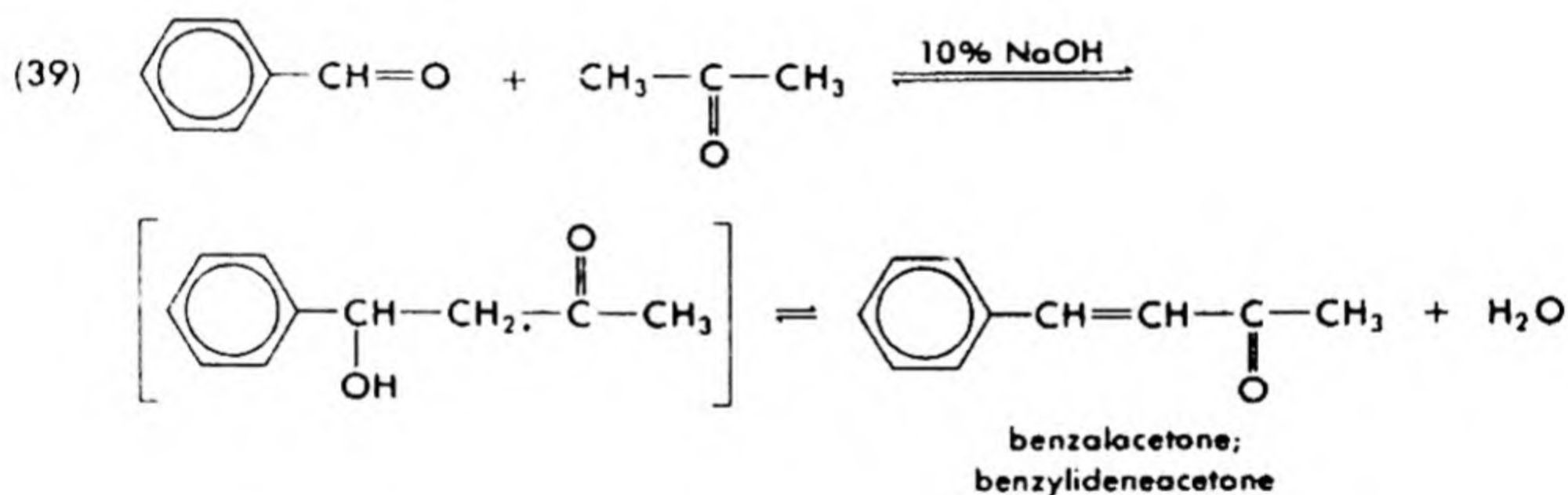


With acid catalysts, dehydration follows addition. For example, acetone heated with hydrochloric acid gives mesityl oxide and with concentrated sulfuric acid forms mesitylene. Acetaldehyde gives crotonaldehyde.



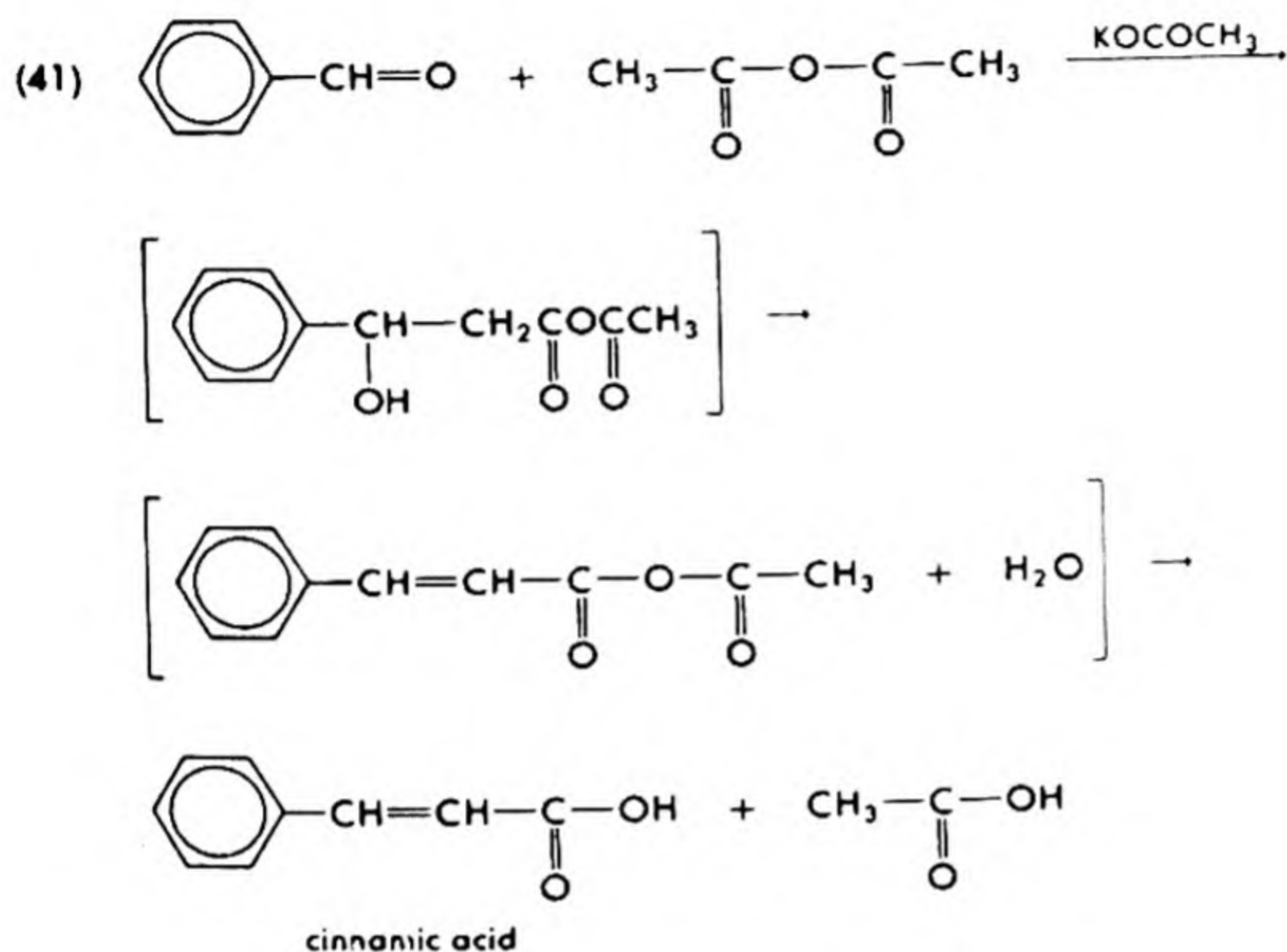


(2) *Claisen-Schmidt Condensations.* The Claisen-Schmidt reaction is a type of condensation which uses an aromatic aldehyde and any ketone or aldehyde which has a methylene group next to the carbonyl group. Aromatic aldehydes have no active methylene groups, but have very reactive carbonyl groups. Because of resonance stabilization in the unsaturated compound, water is lost readily from the initial product to give benzal (benzylidene) ketones and aldehydes. Yields are uniformly high under optimum conditions.

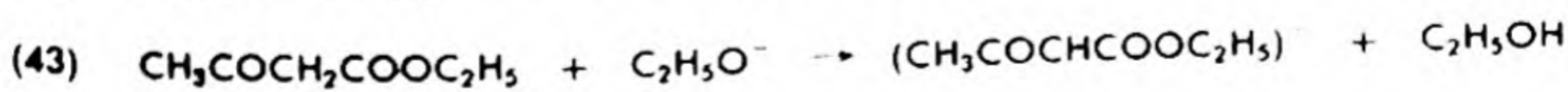


(3) *Perkin Condensations.* The type of condensation discovered by Sir William Perkin and bearing his name is the action of an aromatic aldehyde on an acid anhydride in the presence of the salt of the acid. The aldehyde furnishes the active carbonyl group, the acyl anhydride the

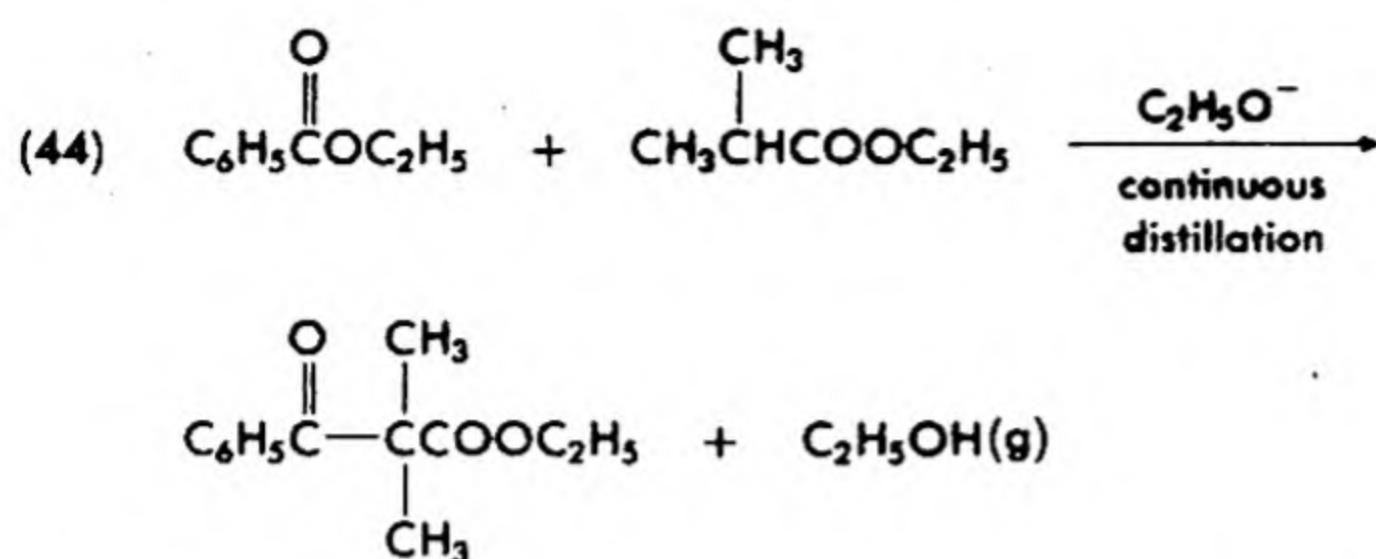
active methylene group. A simple example is the condensation of benzaldehyde with acetic anhydride in the presence of potassium acetate to give a yield of 72% of cinnamic acid. In this reaction, as in the Claisen-Schmidt condensation, the hydroxy group is lost to form water. Thereupon, the water hydrolyzes the anhydride to form the component acids.



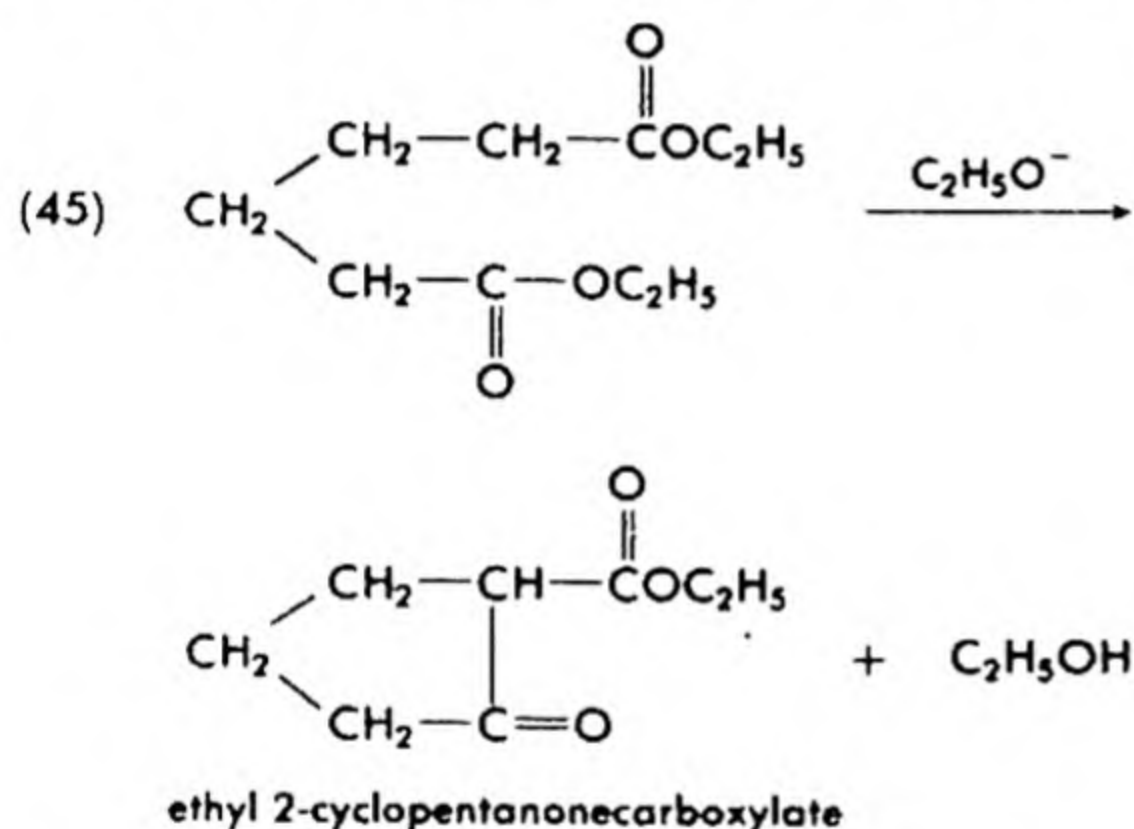
(4) *Claisen Ester Condensations.* Another important type of condensation is the Claisen ester condensation. In this reaction, 2 moles of ester react with each other in much the same way as 2 moles of aldehyde react in the aldol condensation. Since esters are not as reactive as aldehydes, stronger bases are required to catalyze the reaction. The base generally used is a sodium alkoxide, although sodium, sodium hydride, and sodamide are also used. β -Keto esters are stronger acids than alcohols (§10-2D and Table 10-3), so that such condensations are carried to completion by removal of the β -keto ester by ionization (eqs. 42 and 43).



When the resulting β -keto ester has no α hydrogens, the reaction may be forced to completion by removal of one of the products by distillation (eq. 44) or by use of a very strong base, such as sodium triphenylmethide, so that the products are alkoxide ion and triphenylmethane.



Cyclic β -keto esters, such as ethyl cyclopentanonecarboxylate, can be prepared by a base-catalyzed condensation from esters of dicarboxylic acids. This variant is called a *Dieckmann cyclization*. Hydrolysis of this ester, followed by decarboxylation (§21-6B), leads to cyclopentanone.

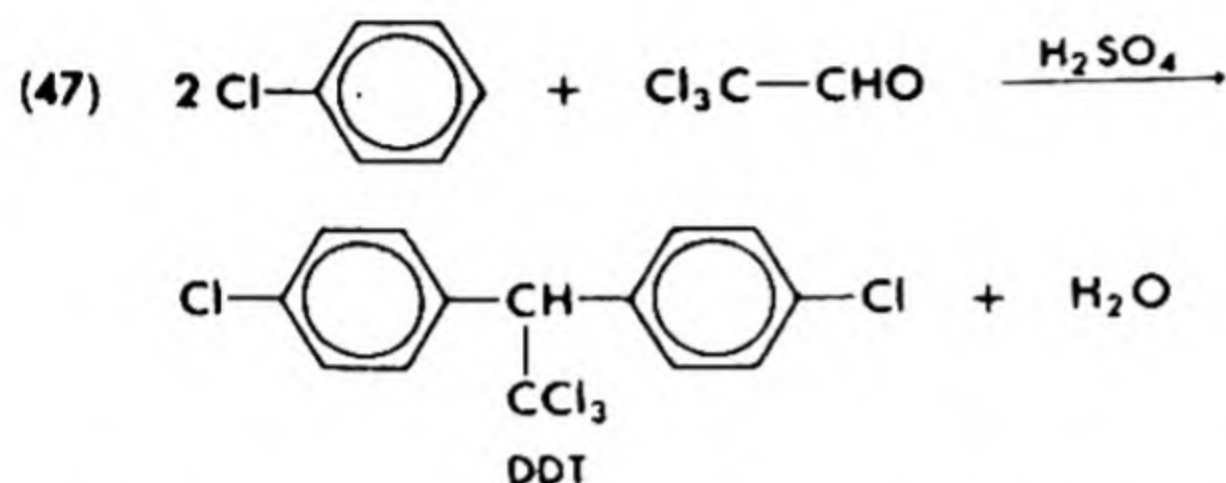
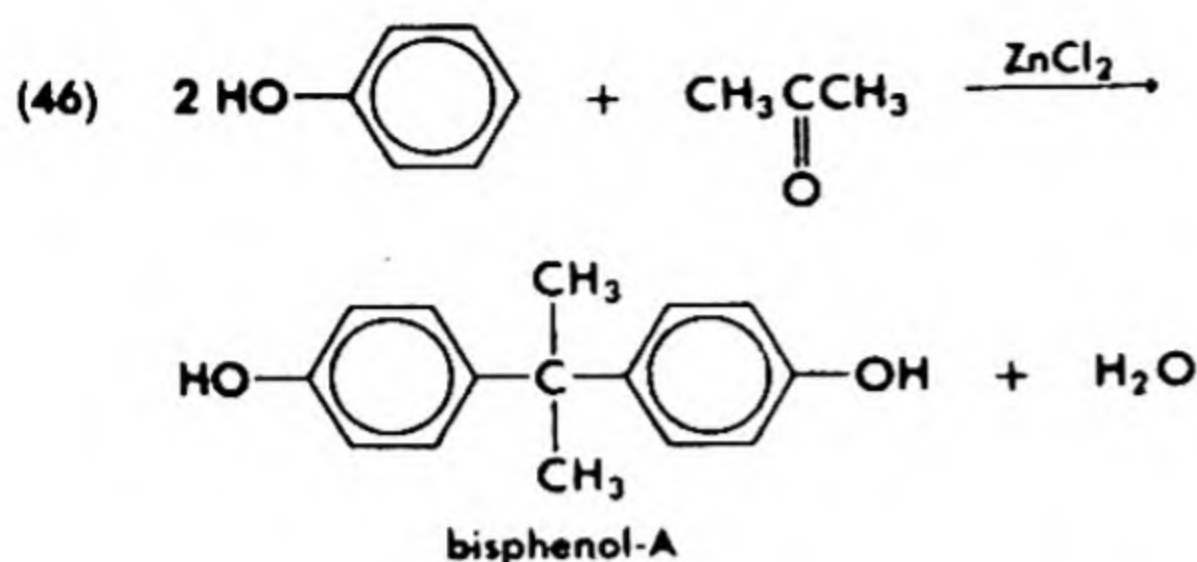


D. Reversibility of Condensation Reactions

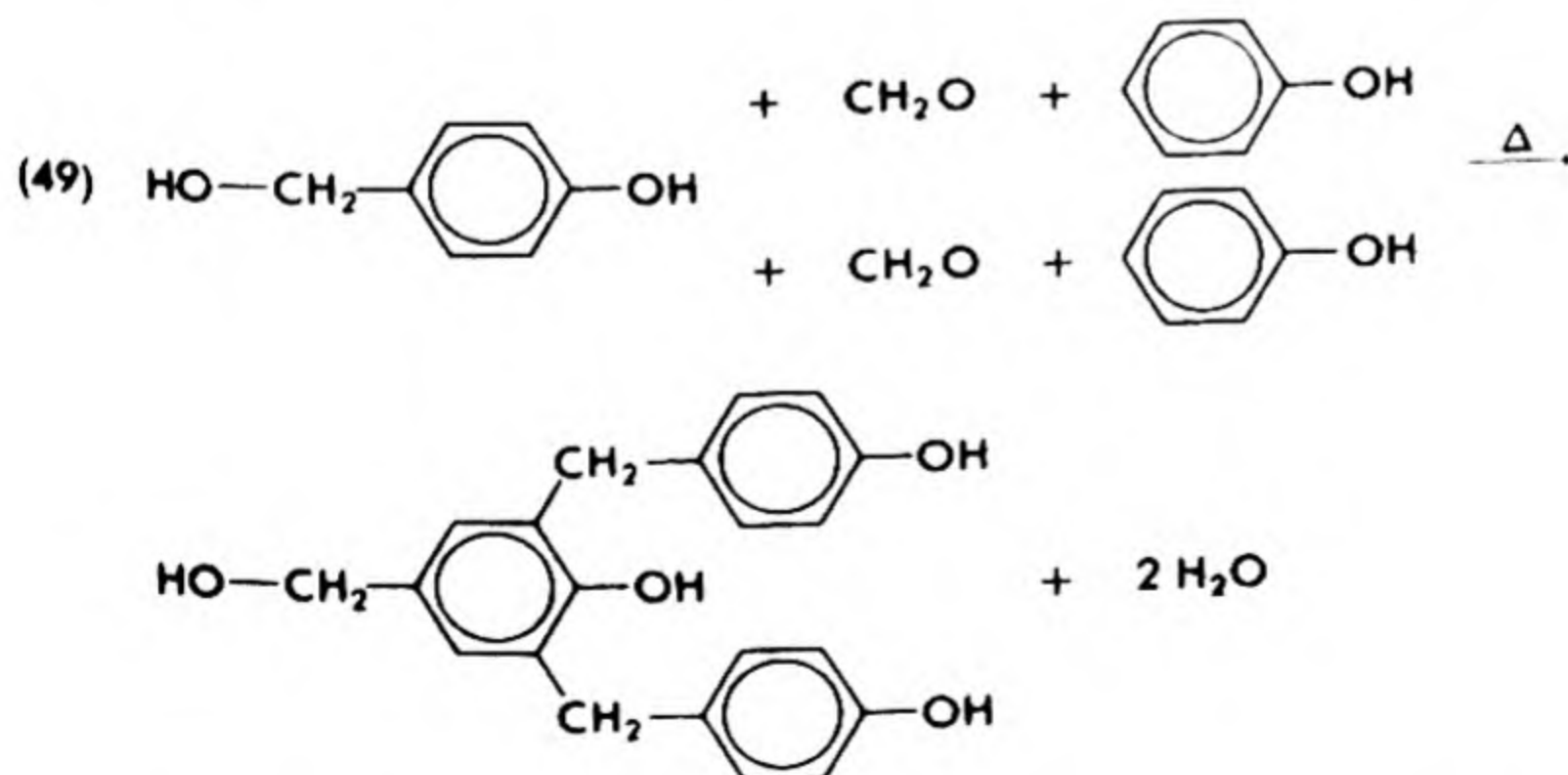
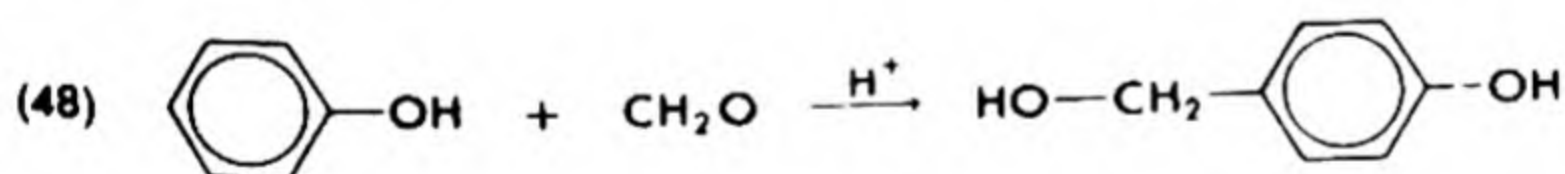
As denoted in some of the sections and equations above, condensation reactions are reversible and in many cases go forward only under special conditions. For many purposes the reverse of the condensation is the desired reaction. Mechanisms are precisely the reverse of the condensation. A case where this is of particular use is in the cleavage of acetoacetic ester (see §21-6B).

21-5 AROMATIC RING CONDENSATIONS

Nucleophilic compounds need not always be active methylene compounds. Phenols and aromatic amines, for example, are nucleophilic at the *ortho* and *para* positions. This type of nucleophile condenses very readily with aldehydes and ketones (eq. 46). Even unactivated aromatic compounds will condense with appropriate aldehydes in the presence of concentrated sulfuric acid. The preparation of DDT (eq. 47) is an example.

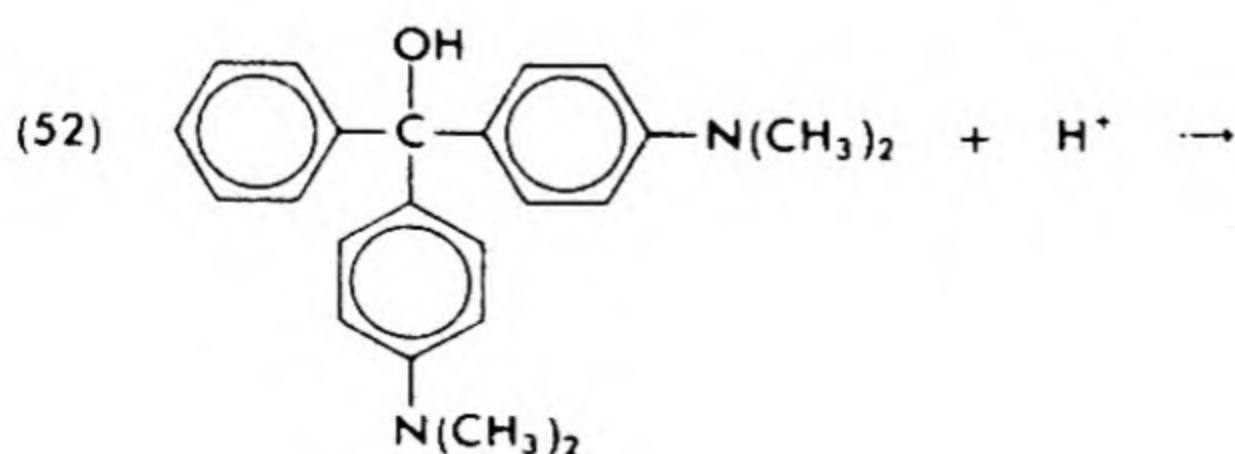
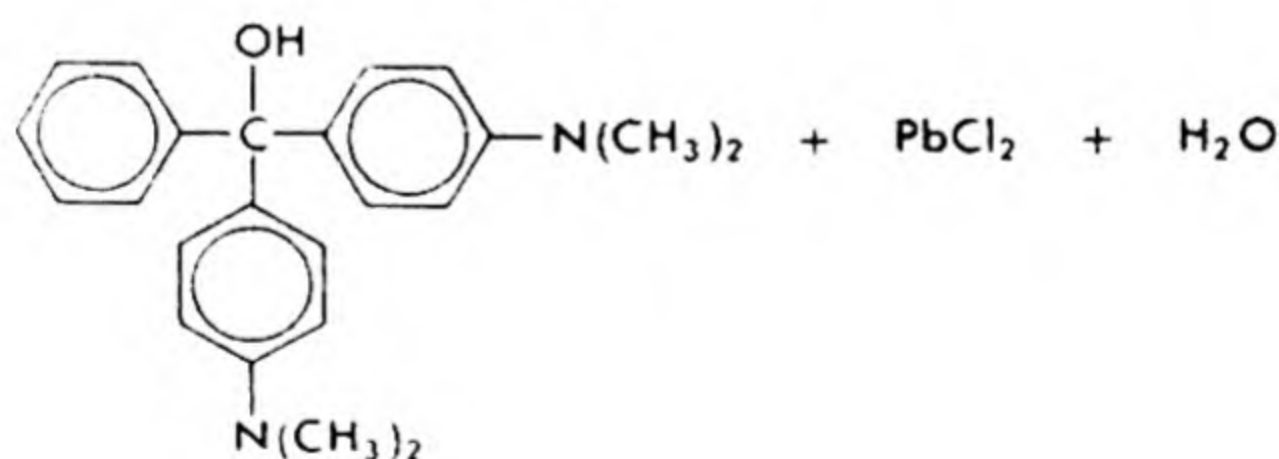
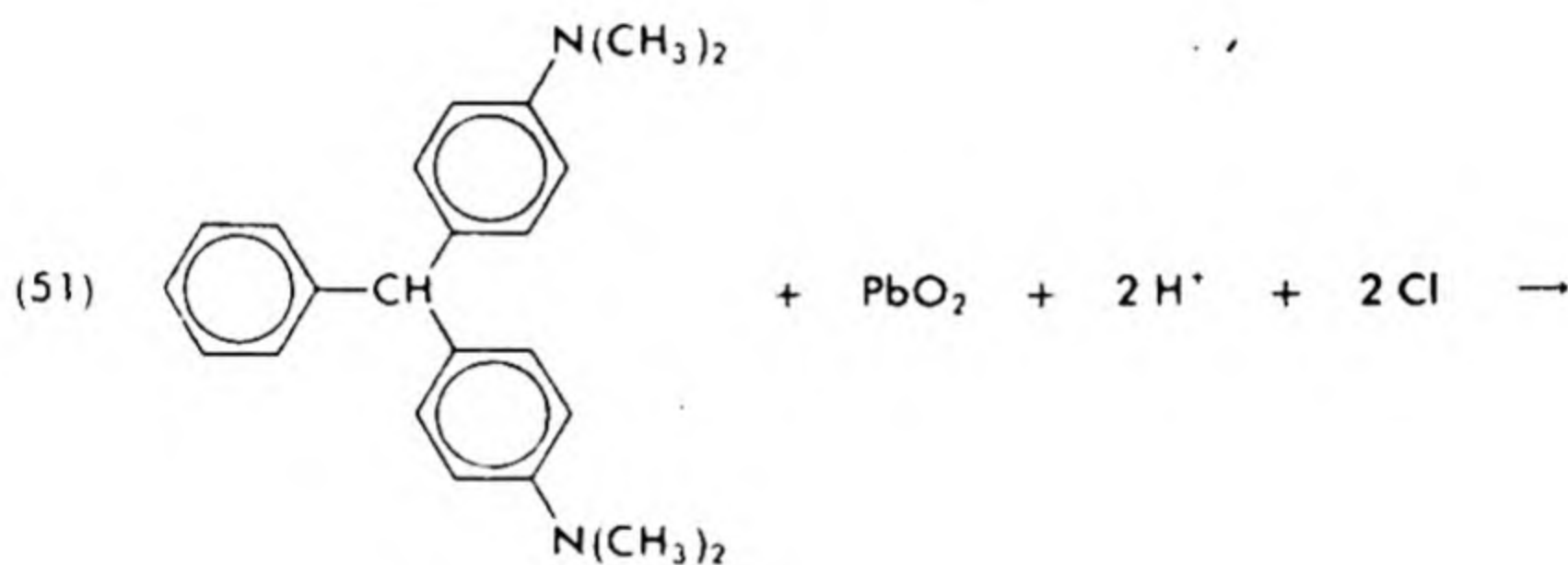
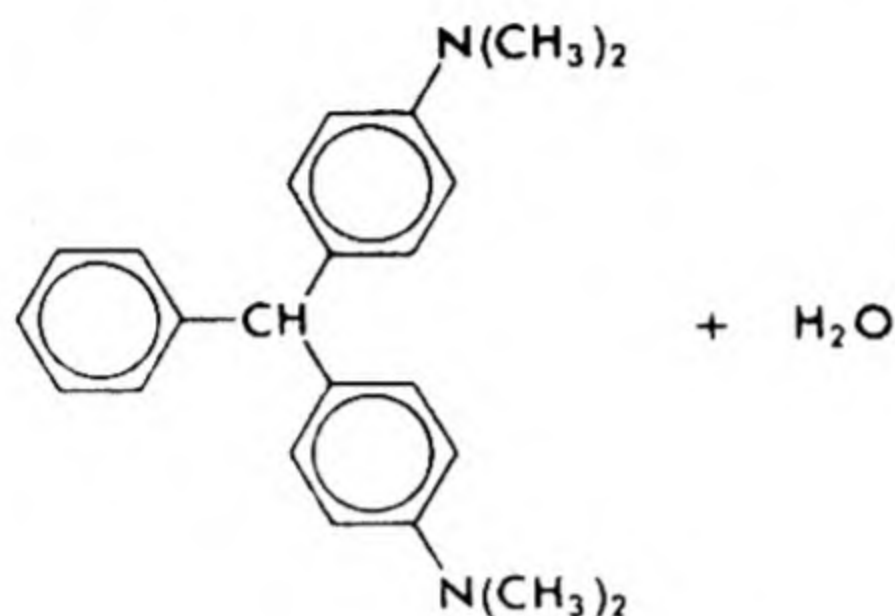
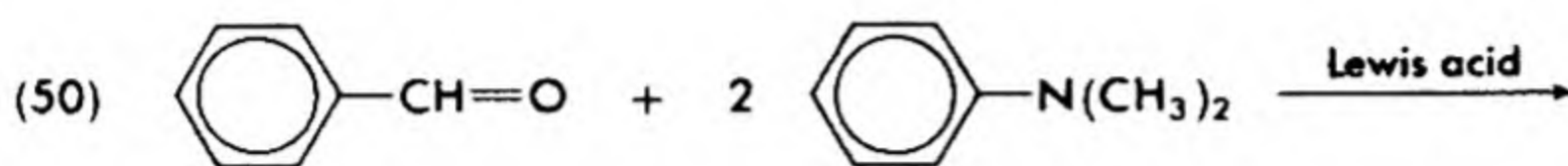


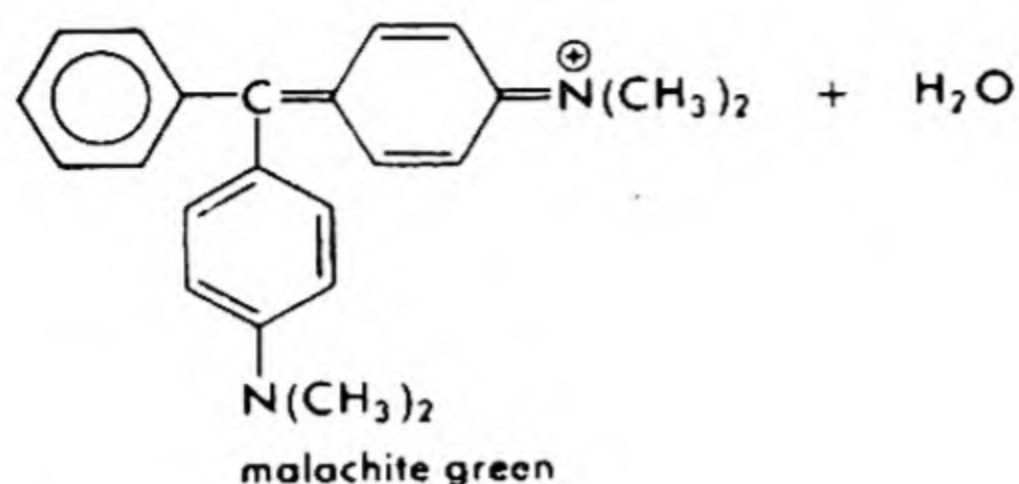
If the reaction between phenol and formaldehyde is very carefully controlled in the presence of a suitable acid catalyst, or simply upon mild heating, *p*-methylophenol can be prepared (eq. 48). However, the reaction is difficult to stop at this point. Advantage is taken of the tendency for more molecules of phenol and formaldehyde to condense in the manufacture of thermosetting resins. The first stages of the reaction are represented in eq. (49).



Similar condensations between benzaldehyde or its derivatives and aromatic amines or phenols have been used to prepare dyes related to

triphenylmethane. Malachite green is made by condensing 2 moles of dimethylaniline with 1 mole of benzaldehyde, followed by oxidation of the methane carbon atom to the carbinol and conversion of the carbinol to the cation (eqs. 50-52).



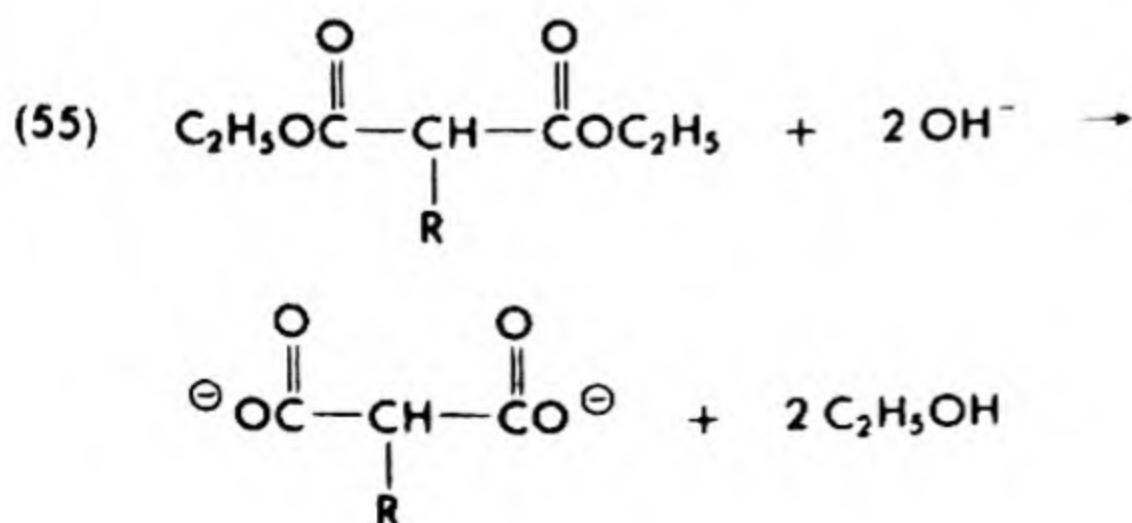
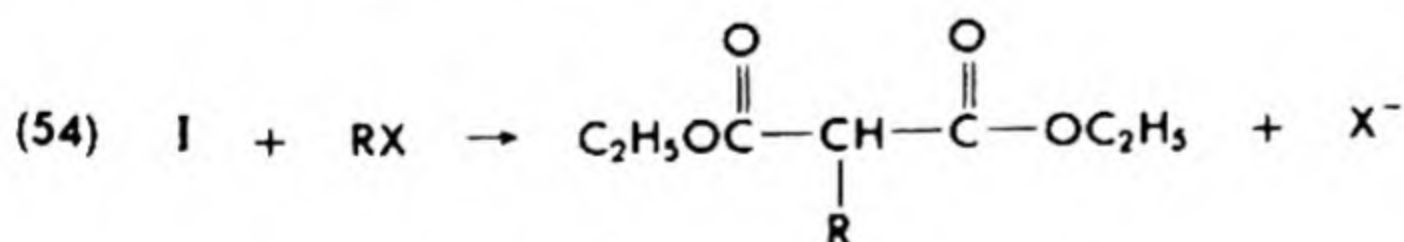
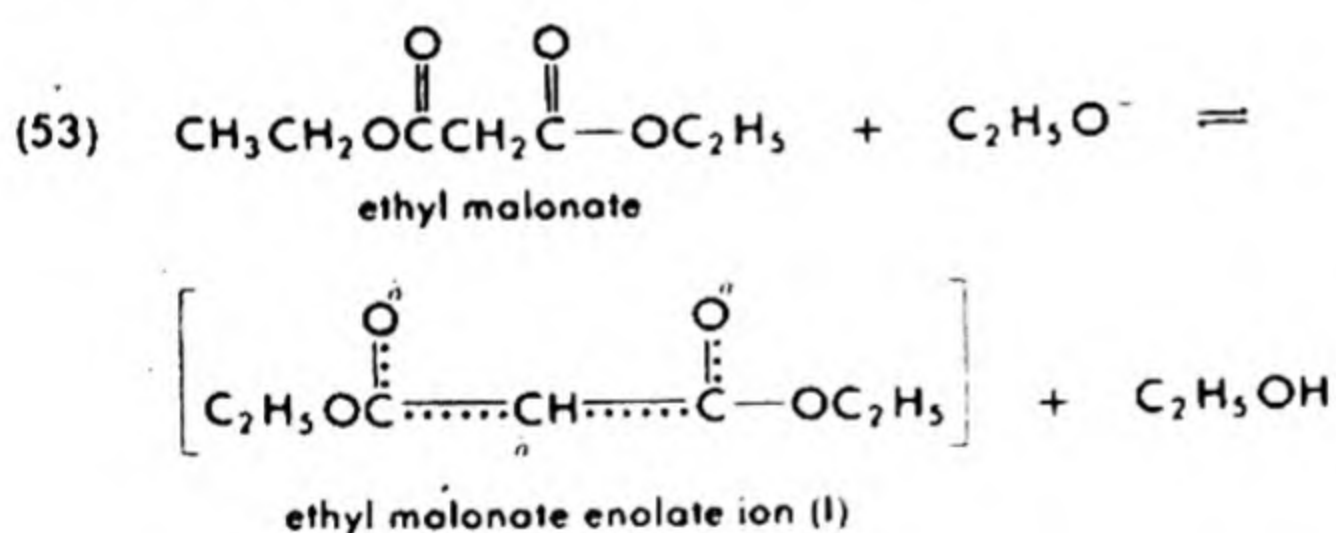


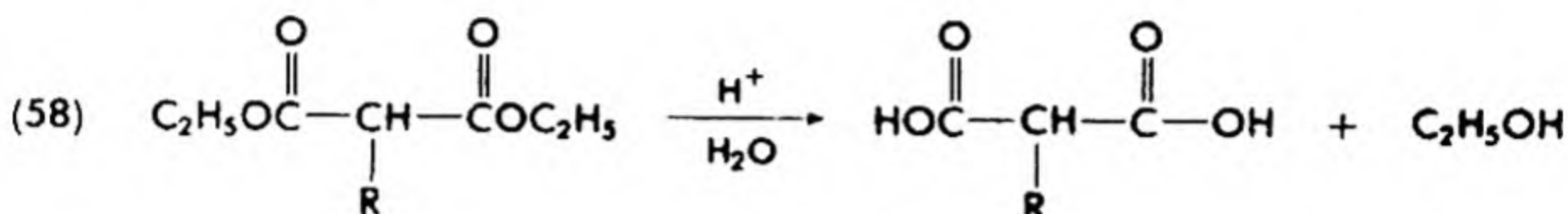
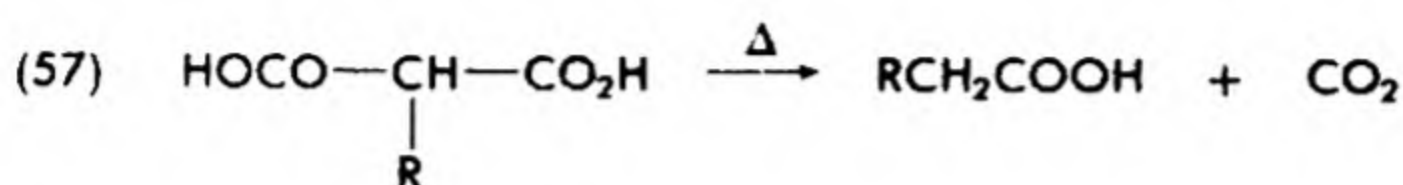
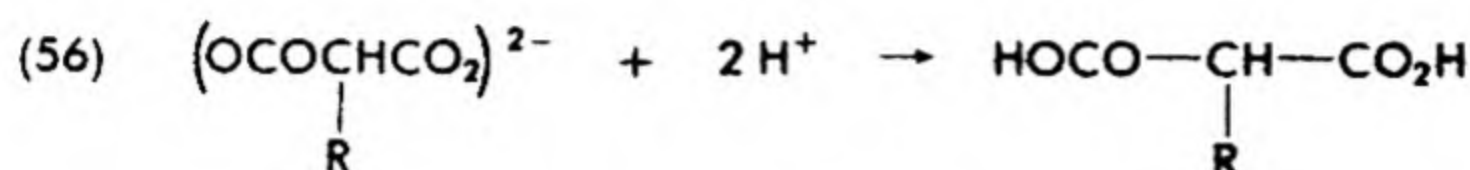
21-6 MALONIC AND ACETOACETIC ESTER SYNTHESSES

The β -carbonyl esters, ethyl acetoacetate and diethyl malonate, have been extensively used in organic syntheses because of their ability to form sodium salts at the active methylene position and because of the several ways such compounds can be hydrolyzed. Alkyl halides react with the enol sodium salts to give carbon-alkylated derivatives, which can be hydrolyzed to give acids or ketones containing the substituent groups.

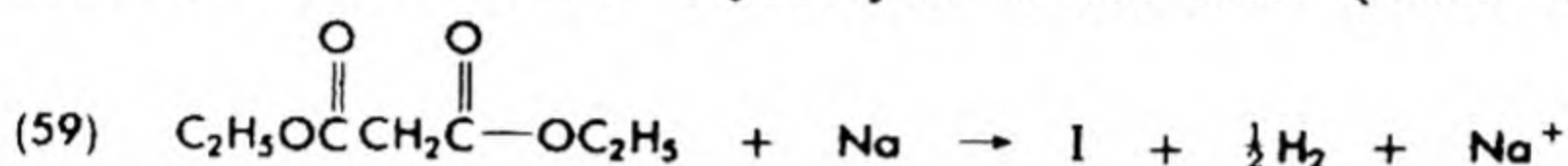
A. Malonic Ester Syntheses of Carboxylic Acids

The preparation of an alkylated acetic acid is shown in eqs. (53) through (58). Treatment of the ester with a strong base (eq. 53) (sodium ethoxide is shown, but sodium hydride is often used) converts malonic ester to its enolate ion.



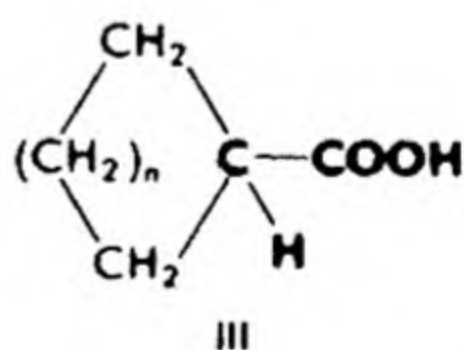
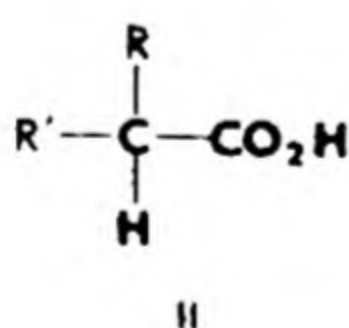


This may also be carried out with sodium metal (eq. 59). Sodiomalonic ester, I, a resonance hybrid with its charge distributed over two oxygen atoms and a carbon atom, is alkylated at the carbon atom to give a substituted malonic ester. Hydrolysis of the ester (either acid- or base-



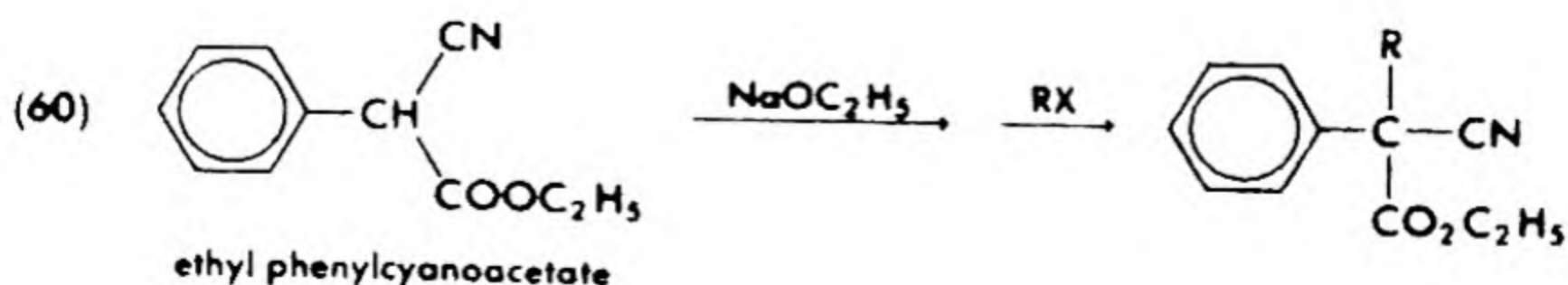
catalyzed) followed by decarboxylation gives the alkylated acetic acid.

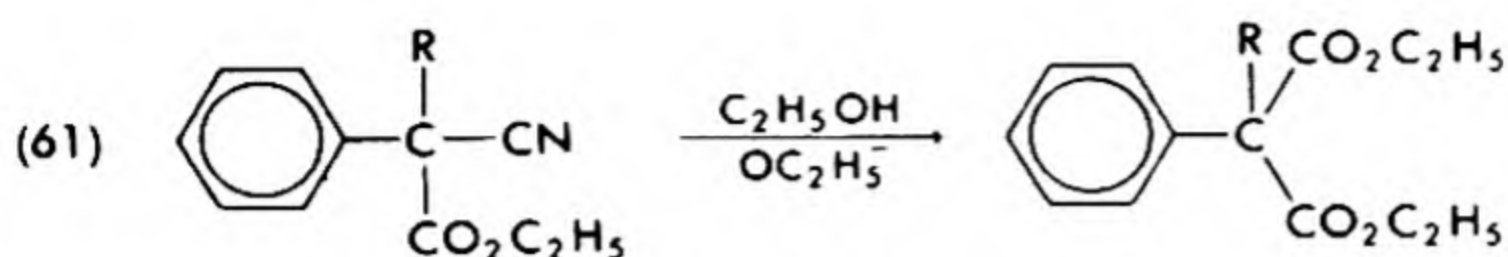
Disubstituted acetic acids can be prepared by introducing another alkyl group following eq. (54) and repeating the series of reactions on the alkylated malonic ester. The same alkyl halide or a different one may be used. The preparation of acetic acids is summarized in II, where the R groups originate from the alkyl halides and the atoms in boldface from the malonic ester.



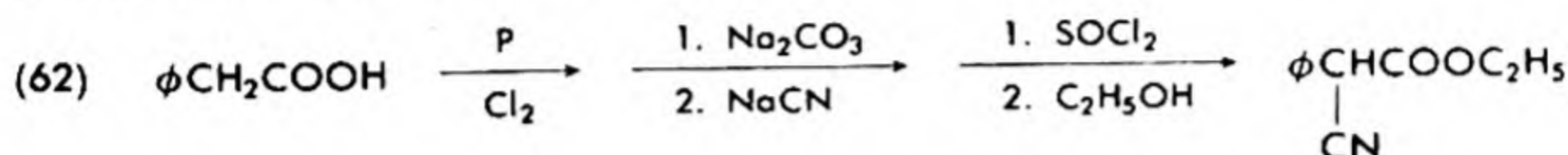
If an alkylene halide is used, two steps similar to eqs. (53) and (54), followed by hydrolysis and decarboxylation give a cyclic product, III.

As most aryl halides are inert to nucleophilic displacement reactions (see §22-6), arylmalonic esters cannot be made from halobenzenes and sodiomalonic ester. Instead one uses ethyl phenylcyanoacetate, which,



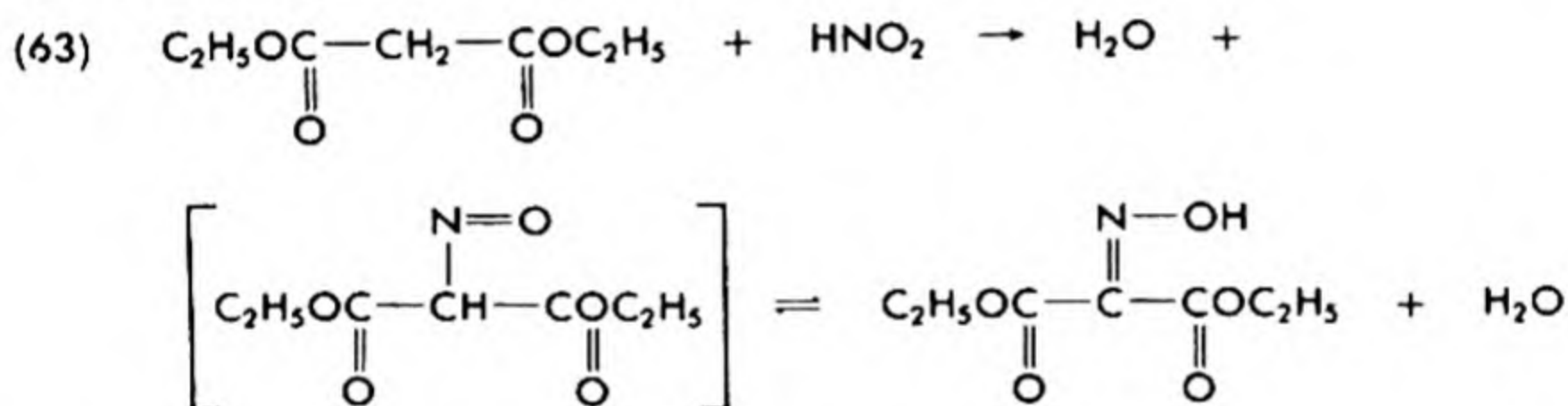


after alkylation, may be alcoholized to give arylalkylmalonic esters. Ethyl phenylcyanoacetate is prepared from phenylacetic acid via α -chlorophenylacetic acid and α -cyanophenylacetic acid.

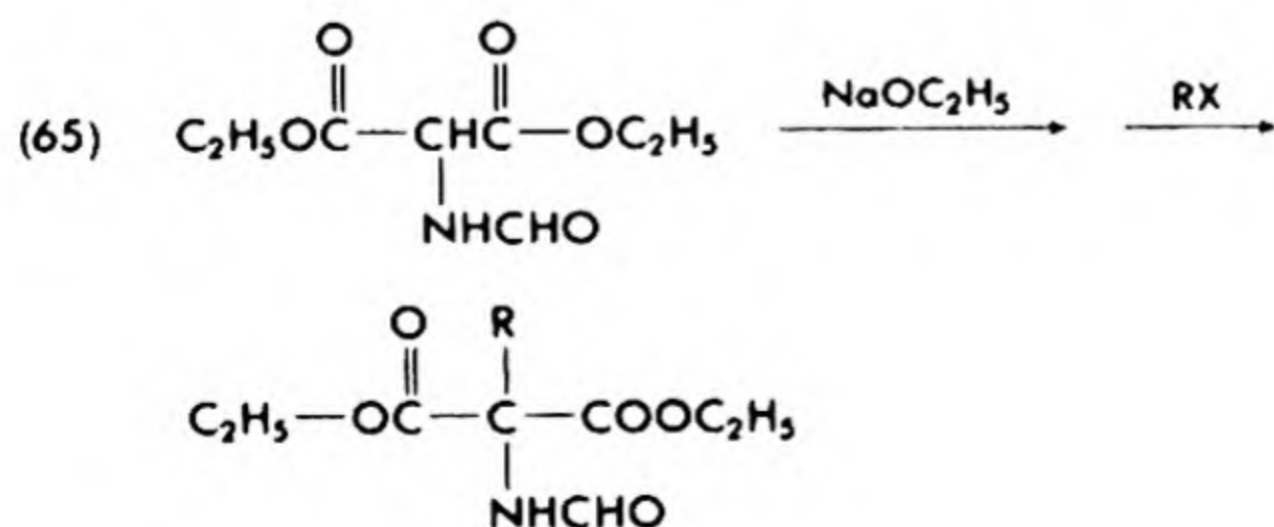
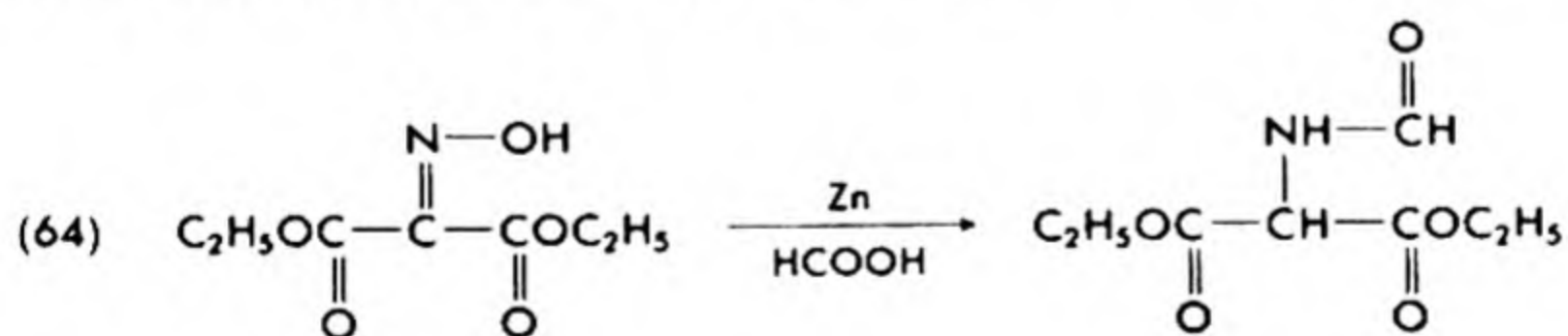


An additional important use for malonic esters is for the preparation of the important class of hypnotics called barbiturates (§42-11).

Malonic ester is extensively used for the preparation of α -amino acids. The very first step is oximation of the active methylene group. Two hydrogen atoms on the group are essential for this step.



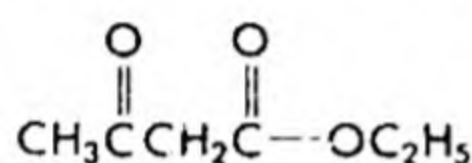
The second methylene hydrogen atom is necessary so that the nitroso compound initially formed (eq. 63) can tautomerize to an oxime. This is then reduced in a second step. The amine produced by the reduction is then formylated, and that product alkylated in the usual manner.



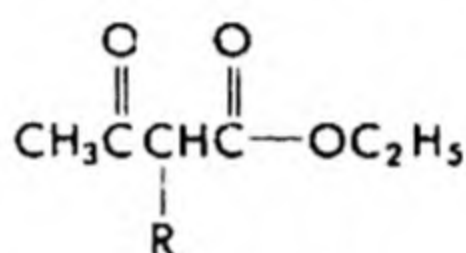
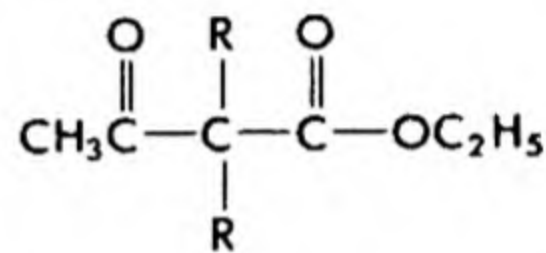
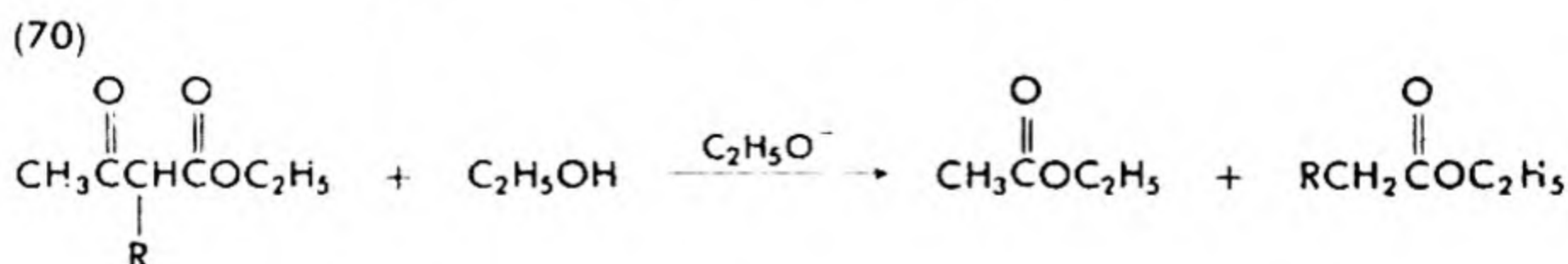
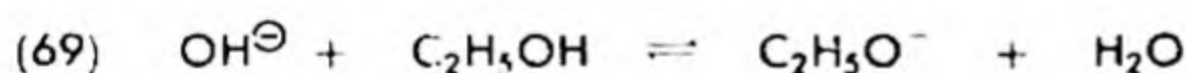
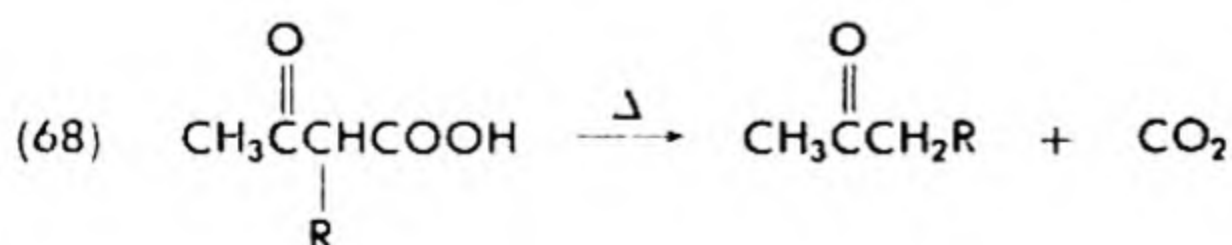
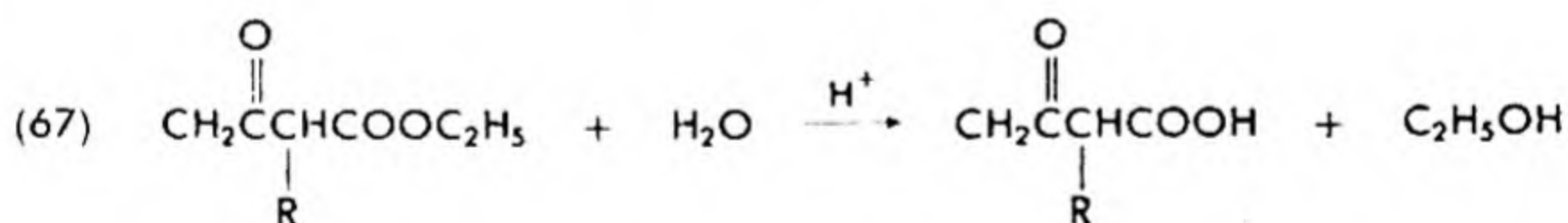
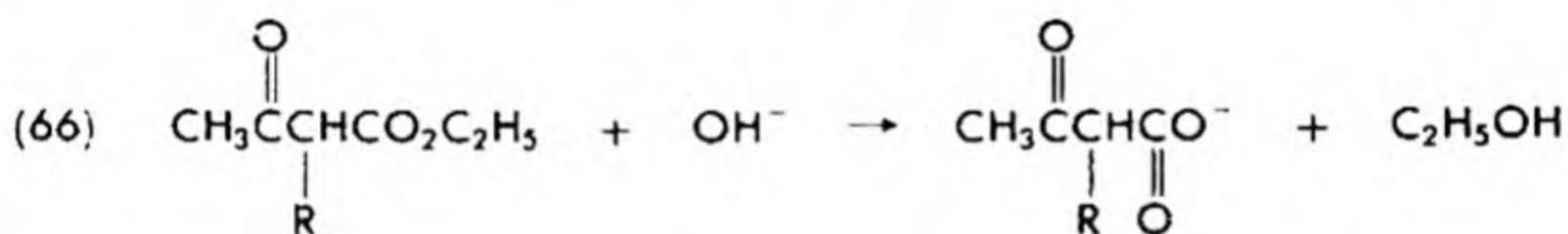
Hydrolysis of the C-alkylated formamido malonate then gives the amino acid. Note, however, that a dialkylated amino acid, $\text{R}_2\text{C}-\text{C}(\text{O})-\text{O}^-$, cannot be prepared by this method, since an amino group in the ester prevents dialkylation.

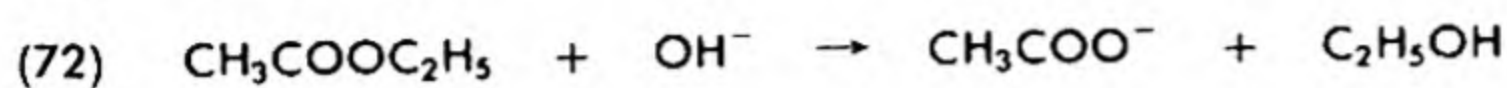
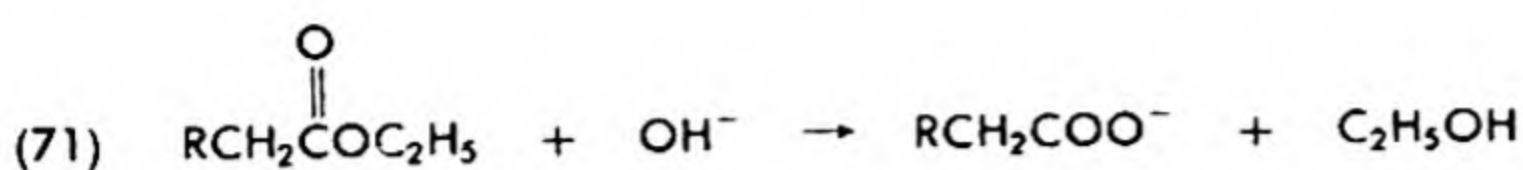
B. Acetoacetic Ester Syntheses of Acids and Ketones

Acetoacetic ester is treated like malonic ester for alkylation, to give monoalkylated products or dialkylated products. However, the fate of the β -keto ester depends on the solvolysis conditions. With acid hydrolysis or with hydrolysis effected by dilute aqueous base, normal ester hydrolysis occurs, (eqs. 66 and 67), giving the acetoacetic acid, which is decarboxylated on warming (eq. 68). As these reactions result in the formation of ketones, treatment of acetoacetic esters with acid or with dilute base has come to be called "ketonic cleavage." Solvolysis with concentrated ethanolic alkali results in the formation of alkylated acetic acids, proceeding by the path represented by eqs. (69) through (72).



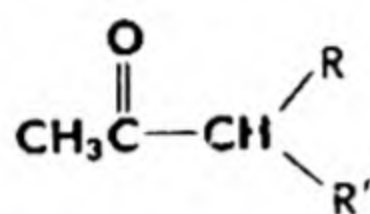
ethyl acetoacetate

monoalkylated
acetoacetic esterdialkylated
acetoacetic ester

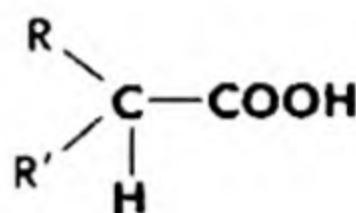


Note that the key in this reaction is the *reverse Claisen condensation* (eq. 69) (see §21-4D). Because the products of the hydrolysis with concentrated ethanolic alkali are salts of alkylated acetic acids, this reaction is generally called "acid cleavage."

Ketones and acids that can be prepared by these routes are indicated in IV and V, with the R groups deriving from alkyl halides and the portion in boldface originating from acetoacetic ester.

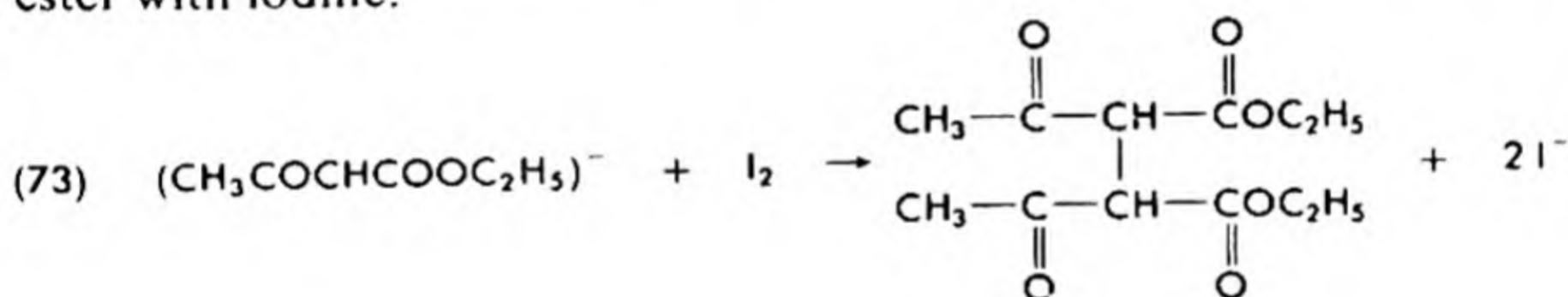


IV



V

To prepare succinic acid derivatives or 1,5-hexanedione derivatives, 2 moles of ester or monoalkylester can be coupled by treating the sodio ester with iodine.

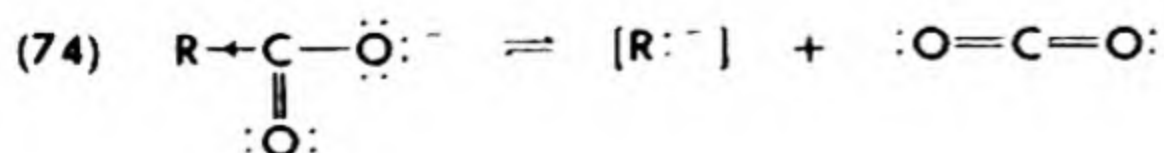


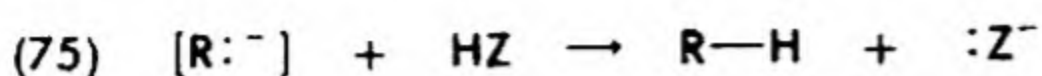
21-7 DECARBOXYLATION REACTIONS

Several examples of decarboxylation were pointed out in connection with the ester syntheses (§21-6A and §21-6B).

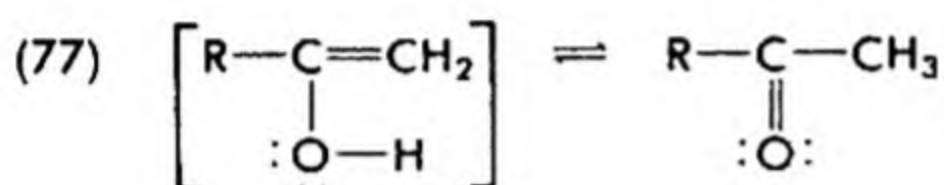
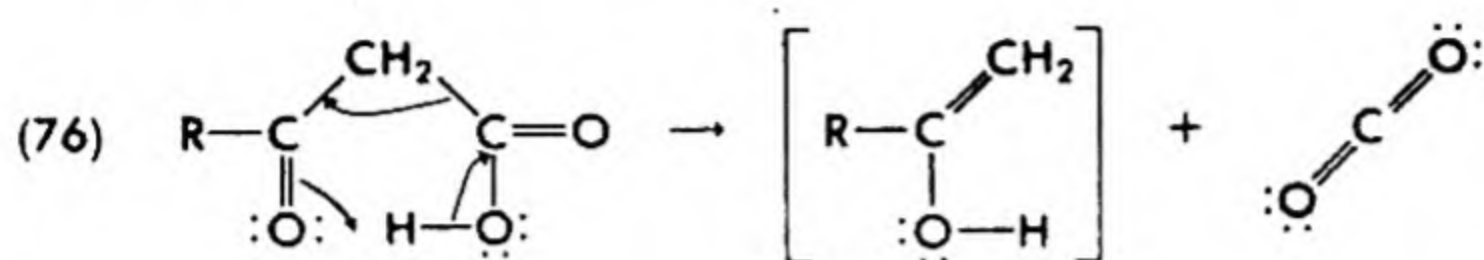
A. Reaction Mechanisms

Electron-withdrawing groups in the acyl radical of a carboxylic acid promote decarboxylation, particularly when they enhance the stability of the carbanion formed when carbon dioxide is eliminated. This suggests that the slow step of decarboxylation is formation of a carbanion by loss of carbon dioxide from a carboxylate ion. Once formed, the carbanion reacts with a hydrogen ion source to give a new carbon-hydrogen bond. In decarboxylations that occur in aqueous solution, the water provides a source of hydrogen ions. In fusion of sodium salts with sodium hydroxide, enough water is formed in the reaction to serve the same purpose.



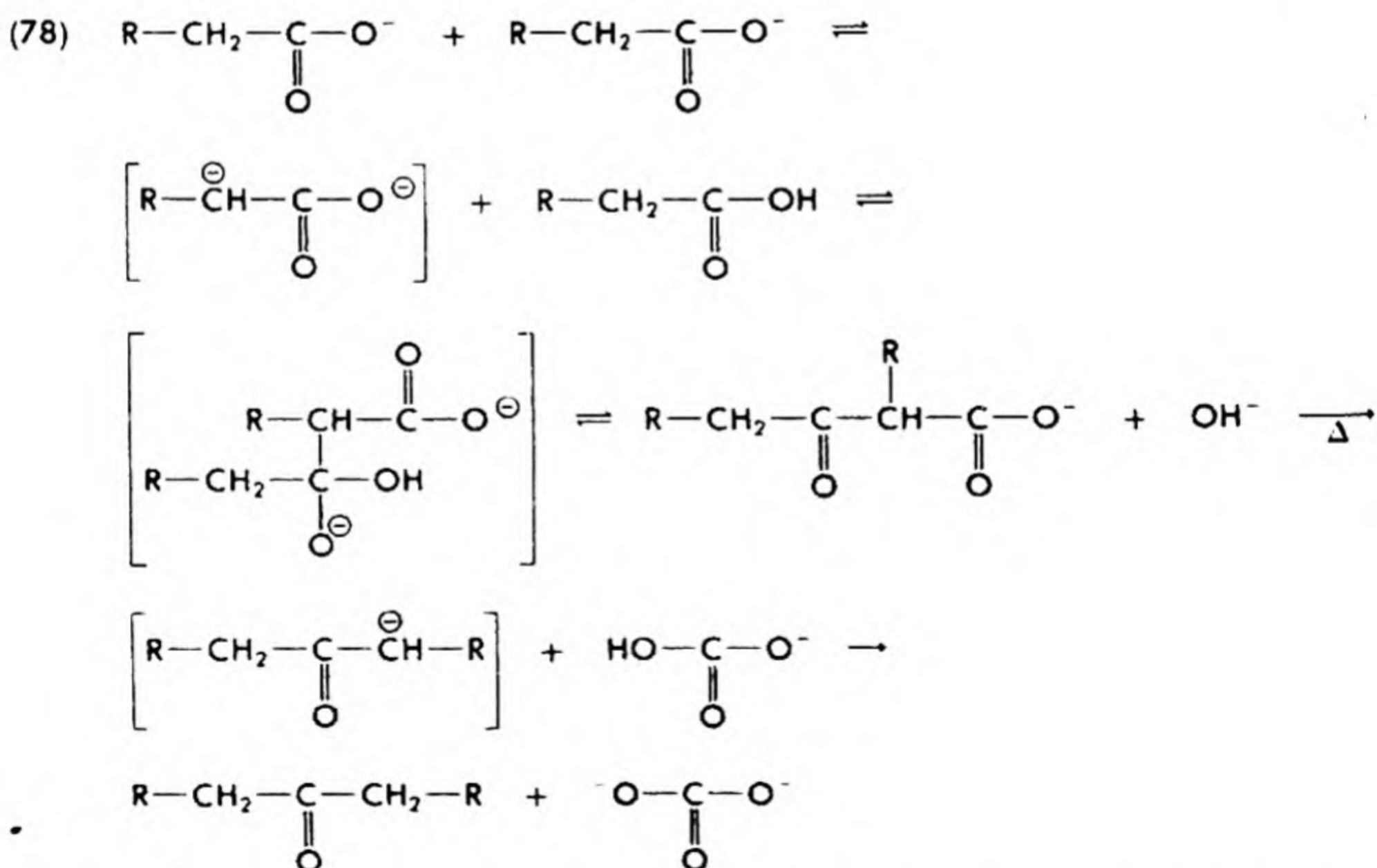


Some decarboxylations occur much more readily under acid conditions than would be expected from this mechanism. Decarboxylation of β -keto acids is an example. The free acid, not its salt, decarboxylates, probably via the following mechanism:



When the acyl radical lacks carbanion-stabilizing groups, decarboxylation is difficult and requires drastic conditions. Much cracking results, since the carbanion stabilizes itself by loss of groups before it can receive a hydrogen ion at the high temperatures involved.

When only the carboxylate ion is present, a reaction similar to condensation followed by decarboxylation occurs. This represents a useful synthesis of ketones.

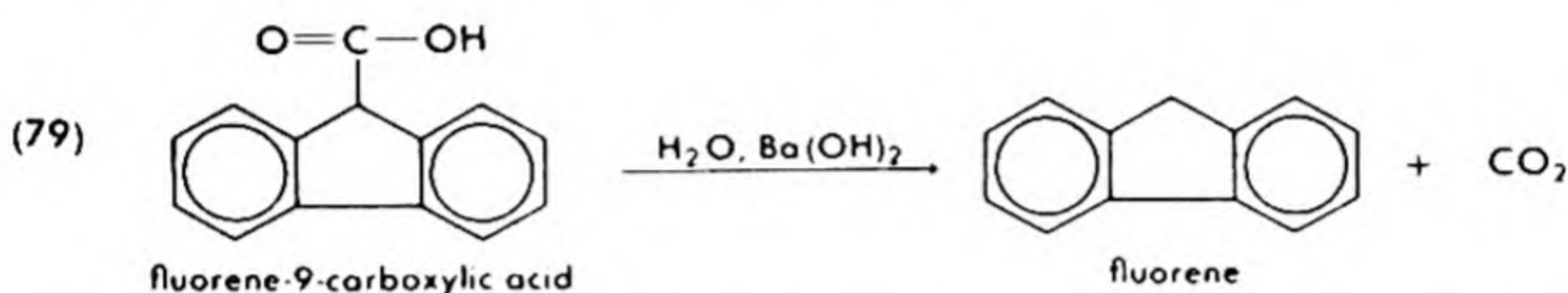


Such reactions are especially easy when cyclization is possible to form five-membered and six-membered rings.

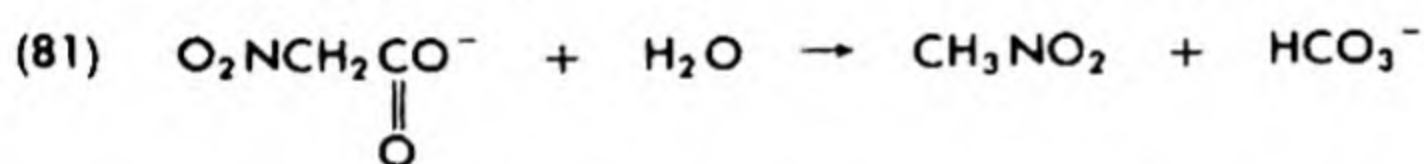
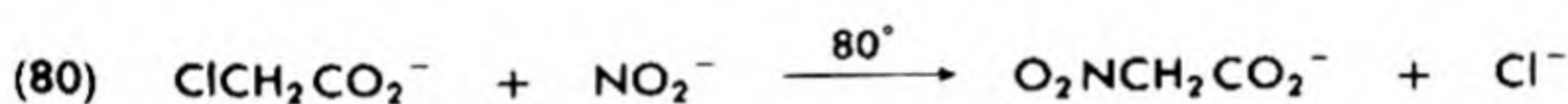
B. Typical Decarboxylations

Formation of methane by fusion of sodium acetate with soda lime is a common laboratory exercise. This is the only alkane that can be prepared in reasonable yield and purity by decarboxylation, however. Butanoic acid is reported to give only 17% propane, along with 7% ethane, 39% methane, 31% hydrogen, and 6% propylene and traces of ethylene.

Decarboxylation of aromatic acids, particularly polynuclear acids, occurs much more smoothly. The acid itself can be heated with copper powder if its boiling point is sufficiently high. Fluorene-9-carboxylic acid decarboxylates readily by boiling in slightly alkaline solution.

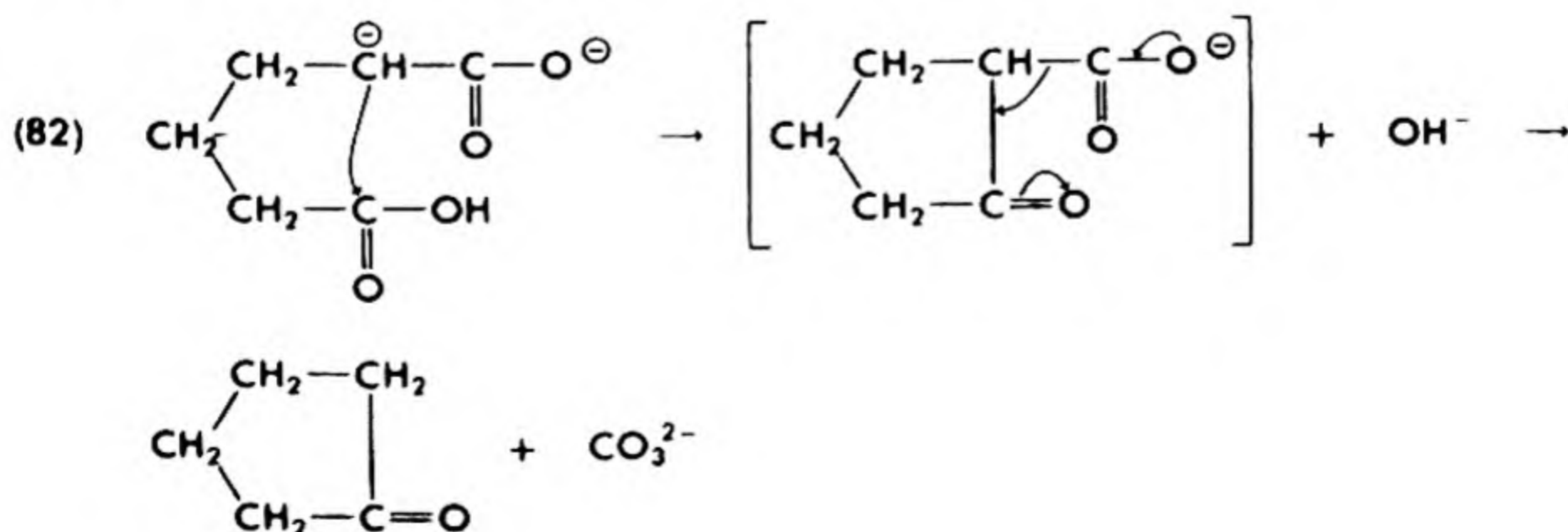


The effect of a nitro group is shown in the spontaneous decarboxylation of nitroacetate ion in the preparation of nitromethane from chloroacetic acid.



Generally, better yields of ketones are obtained from calcium salts than sodium salts, perhaps because of the proximity of the ions attached to the calcium ion, or perhaps even because the semicovalent calcium salt may have the anions oriented so as to favor the condensation step.

The geometry of adipic and pimelic acids favors cyclization to form ketones when their calcium or barium salts are heated (eq. 82). (See eq. 78 for the complete mechanism.)



Excellent yields of the ketones are obtained by decarboxylation of the acids in the presence of catalytic amounts of barium hydroxide or barium carbonate. Yields of 75–80% of cyclopentanone are reported using this method.

SUPPLEMENTARY READINGS

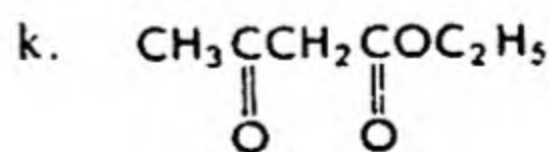
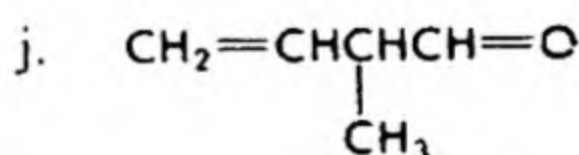
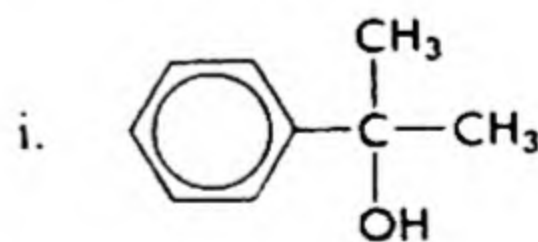
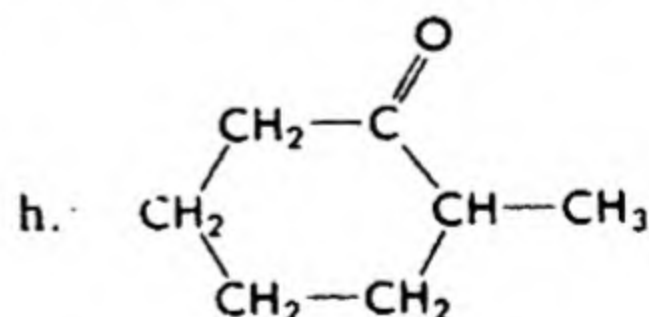
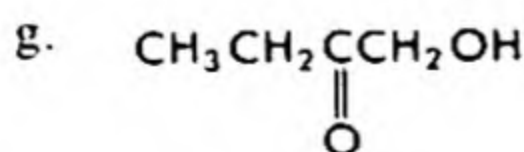
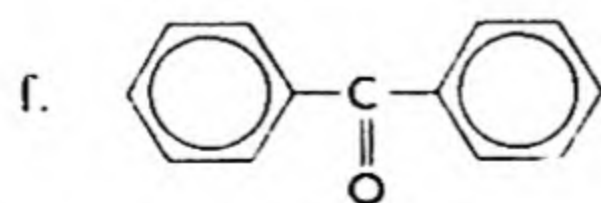
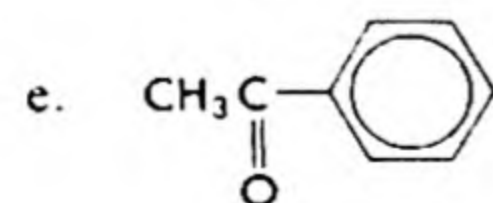
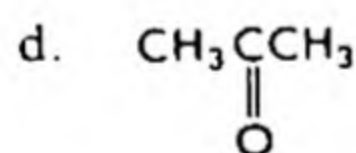
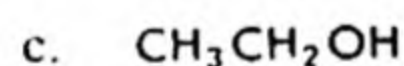
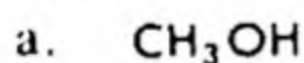
- Gould, E. S., *Mechanism and Structure in Organic Chemistry*, Holt-Dryden, New York, 1959, Chapter 10, "Carbanions and Enolization."
- Hauser, C. R., and B. E. Hudson, Jr., "The Acetoacetic Ester Condensation and Certain Related Reactions," *Org. Reactions*, **1**, 266–302, (1942).
- Hauser, C. R., F. W. Swamer, and J. T. Adams, "The Acylation of Ketones to Form β -Diketones or β -Keto Aldehydes," *Org. Reactions* **8**, 59–196 (1954).
- Hine, J., *Physical Organic Chemistry*, 2nd Ed., McGraw-Hill, New York (1962), pp. 302–310 (concerning decarboxylation).
- Johnson, J. R., "The Perkin Reaction and Related Reactions," *Org. Reactions* **1**, 210–265 (1942).

QUESTIONS AND PROBLEMS

1. Define condensation reaction. Give the restricted sense of the term.
2. Write equations to illustrate the following reactions. Use structural formulas of actual compounds not given in the text.

- | | |
|-----------------------|-------------------------------|
| a. aldol condensation | c. Claisen ester condensation |
| b. Perkin reaction | d. Claisen-Schmidt reaction |

3. Pick out from the following list those compounds which undergo the haloform reaction. Write equations for the reactions involved, including those that do not yield haloform. Use sodium hydroxide and bromine as reagents.



4. Write equations for the reactions that occur between the substances listed together below. Use structural formulas of organic compounds and indicate essential special conditions.

- | | |
|---|---|
| a. α -ethylpimelic acid and barium carbonate | d. butyric acid, bromine, and a trace of red phosphorus |
| b. barium cyclobutanecarboxylate | e. ethyl acetate and bromine |
| c. 3-phenylheptanedioic acid and barium carbonate | |

5. Show by outline how the following compounds can be prepared in good yield from the suggested starting materials. Use structural formulas for organic compounds. Indicate inorganic reagents and essential conditions.

- ethyl acetoacetate from ethanol as the only organic raw material
- crotonaldehyde from acetaldehyde as the only organic raw material
- ethyl cinnamate from benzaldehyde and ethanol
- mesityl oxide from propylene as the only organic raw material
- β -hydroxybutyraldehyde from ethanol as the only organic raw material
- dianisalacetone from anisaldehyde and isopropyl alcohol
- 2-methyl-3-*p*-tolyl-2-propenoic acid from *p*-tolualdehyde and propionic acid
- acetylacetone from propylene and ethyl acetate
- β -nitrostyrene from benzaldehyde and methyl bromide
- tetraphenylcyclopentadienone from benzil and dibenzyl ketone
- 1-nitropropane from butyric acid
- 1,4-dimethylcyclopentanone from malonic acid and methanol
- 1,3-butanediol from ethanol and acetic acid
- 2-methyl-2,4-pentanediol from acetone

6. Show how the following compounds can be prepared from ethyl malonate and other necessary reagents. Use structural formulas for organic intermediates. Outline form is permissible.

- | | |
|---|---|
| a. hydrocinnamic acid | f. 2-methylcyclopropane-1-carboxylic acid |
| b. δ -bromovaleric acid | g. <i>n</i> -valeric acid |
| c. DL- α -alanine (α -aminopropionic acid) | h. cyclobutanecarboxylic acid |
| d. leucine (α -aminoisocaproic acid) | i. 2-amino-2-ethylbutanoic acid |
| e. 2-methyl-3-phenylpropanoic acid | j. 2-aminopentanedioic acid |

7. Show how the following compounds can be prepared from ethyl acetoacetate and other necessary reagents. Use structural formulas for organic intermediates. Outline form is permissible.

- | | |
|------------------------------------|--|
| a. isobutyric acid | g. 3,4-dimethylhexane-2,5-dione |
| b. glutaric acid | h. methyl- β -phenylethylcarbinol |
| c. succinic acid | i. β -(<i>p</i> -bromophenyl)propionic acid |
| d. methyl cetyl ketone | j. 2-ethylpentanoic acid |
| e. methyl <i>sec</i> -butyl ketone | k. 3-methylhexanoic acid |
| f. 2,6-heptanedione | |

- | | |
|--|--------------------------------------|
| l. cyclopropanecarboxylic acid | p. cyclohexane-1,2-dicarboxylic acid |
| m. 1,4-diacetylcyclohexane | |
| n. methyl cyclobutyl ketone | |
| o. tyrosine (α -amino- β - <i>p</i> -hydroxy-phenylpropionic acid) | |

REVIEW PROBLEMS

1. Write equations for any reactions that occur in the reagent mixtures below. Use structural formulas for organic compounds. Indicate essential conditions. If no reaction occurs, write the formulas of the reagents, the arrow and "NR."

- | | |
|---|---|
| a. benzaldehyde and acetic anhydride | g. phenol and hydroxylamine |
| b. butanone, iodine, and potassium hydroxide | h. benzaldehyde and 2-methylcyclohexanone |
| c. ethyl α -acetobutyrate and dilute sulfuric acid | i. dimethylketene and methanethiol |
| d. ethyl acetoacetate and bromine | j. acetone and ethanol |
| e. ketene and methyl iodide | k. benzoic acid and hydrochloric acid |
| f. diethylketene and barium hydroxide | l. aceto- <i>p</i> -toluidide and ethanol |

2. Show how the compounds listed can be prepared in acceptable yield from the suggested starting materials. Use structural formulas for organic compounds. Indicate reagents and essential conditions.

- lactic acid from ethanol and inorganic compounds
- acetamide from ethanol
- p*-nitroaniline from benzene
- 2-methylcyclopropane-1-carboxylic acid from propylene and diethyl malonate
- methyl cyclopropyl ketone from ethanol as the only organic raw material
- 2-hydroxy-3-pentenoic acid from ethanol as the only organic raw material
- 3-ethyl-2-pentanone from ethanol as the only organic raw material
- 2-amino-4-hydroxybutanenitrile from ethanol, formaldehyde, and inorganic compounds
- methyl methacrylate from acetone and methanol
- N*-methyl-*N,N'*-diphenylurea from aniline and methyl sulfate
- n*-butyl α -bromobutyrate from *n*-butyl alcohol as the only organic raw material

3. Explain, using formulas or equations, what is meant by the following terms.

- | | |
|---------------------------|---------------------------|
| a. protective acetylation | c. active methylene group |
| b. condensation reaction | d. enolization |

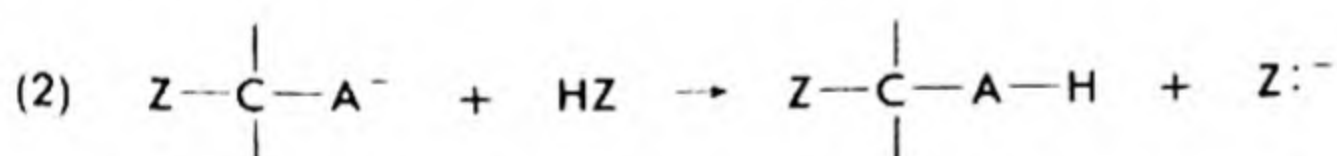
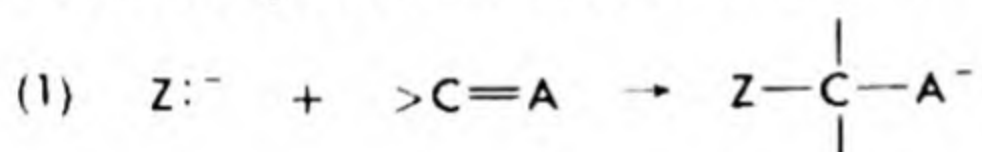
22

Nucleophilic Reactions at Unsaturated Carbon

IV. Reactions at Carbon-Carbon Multiple Bonds: Conjugate Addition, Vinylation, and Nucleophilic Aromatic Substitution

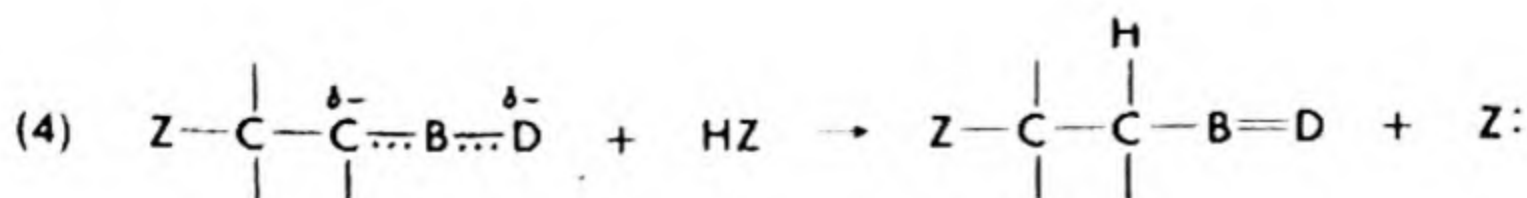
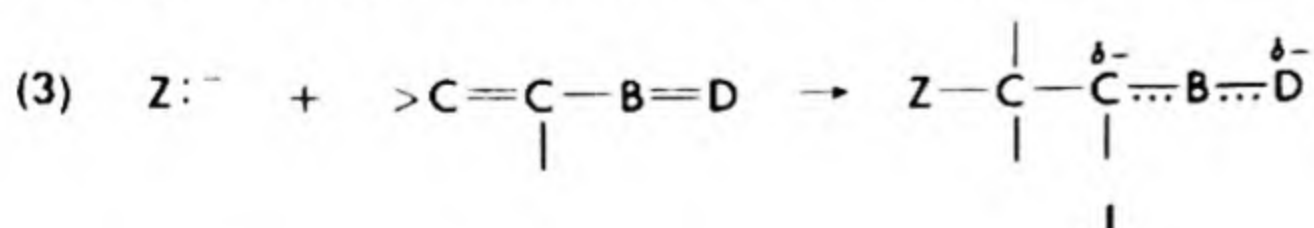
22-1 INTRODUCTION

Chapter 18 describes the addition of nucleophilic reagents to polar unsaturated bonds, such as carbonyl and cyano groups, (eqs. 1 and 2). Such reactions proceed at reasonable rates, because the rate of reaction (1) is



influenced favorably by the ability of the atom A (usually oxygen or nitrogen) to assume a negative charge. Unless a carbon atom has one or more very strongly electron-attracting groups attached to it, it is loath to accept the function of the atom A in eq. (1). Nucleophilic additions then occur only under unusual conditions with unactivated olefins.

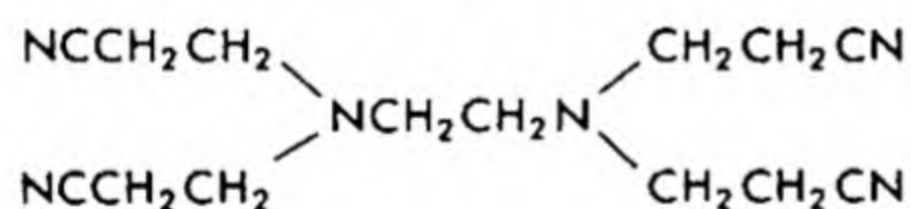
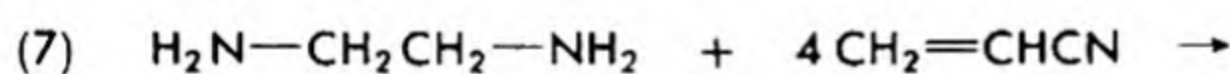
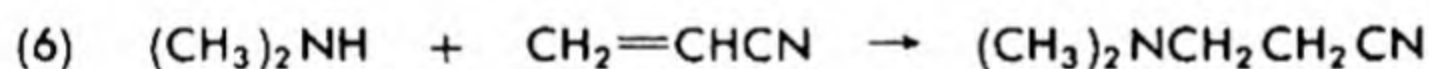
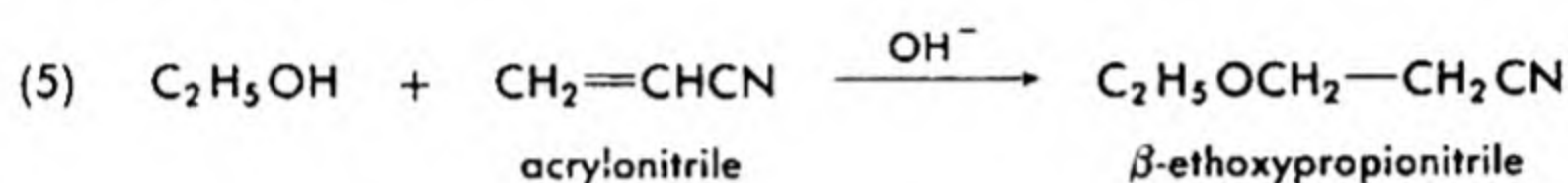
However, when one has a highly fluorinated olefin, or an ethylenic double bond conjugated with an electron sink, as for example, α,β -unsaturated aldehydes, ketones, esters or nitriles, nucleophilic addition goes readily. The general course of the reaction is as follows:



One should note that the intermediate, I, in the addition reaction (eq. 3) is analogous to that involved in nucleophilic substitution reactions (§17-1) and that those functions ($B=D$) which promote reactivity in substitution also promote it in addition. The mechanistic details make clear why *anti-Markovnikoff* (§14-2B) addition is observed.

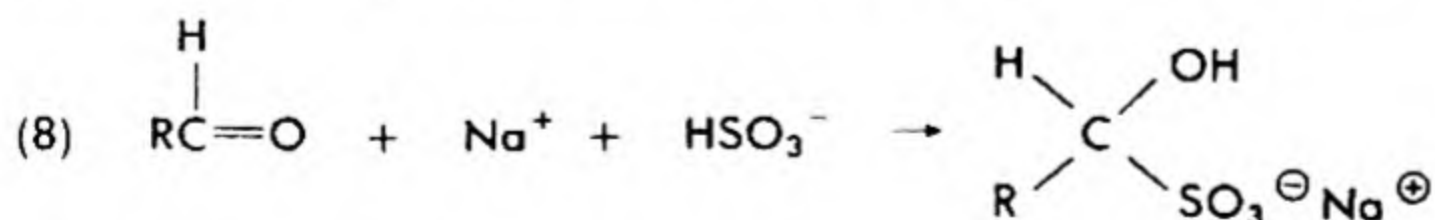
22-2 ADDITIONS TO ACRYLONITRILE. CYANOETHYLATION

Among the most common of the unsaturated reagents used in nucleophilic addition is acrylonitrile. In the presence of catalytic amounts of strong bases, it can add water, alcohols, mercaptans, ammonia, and amines. Ammonia and amines do not require added bases, but act as their own catalysts. Examples are given in eqs. (5) and (6). When more than one active hydrogen is present, cyanoethylation can continue until all are replaced. Thus, ethylenediamine reacts with 4 moles of acrylonitrile (eq. 7).

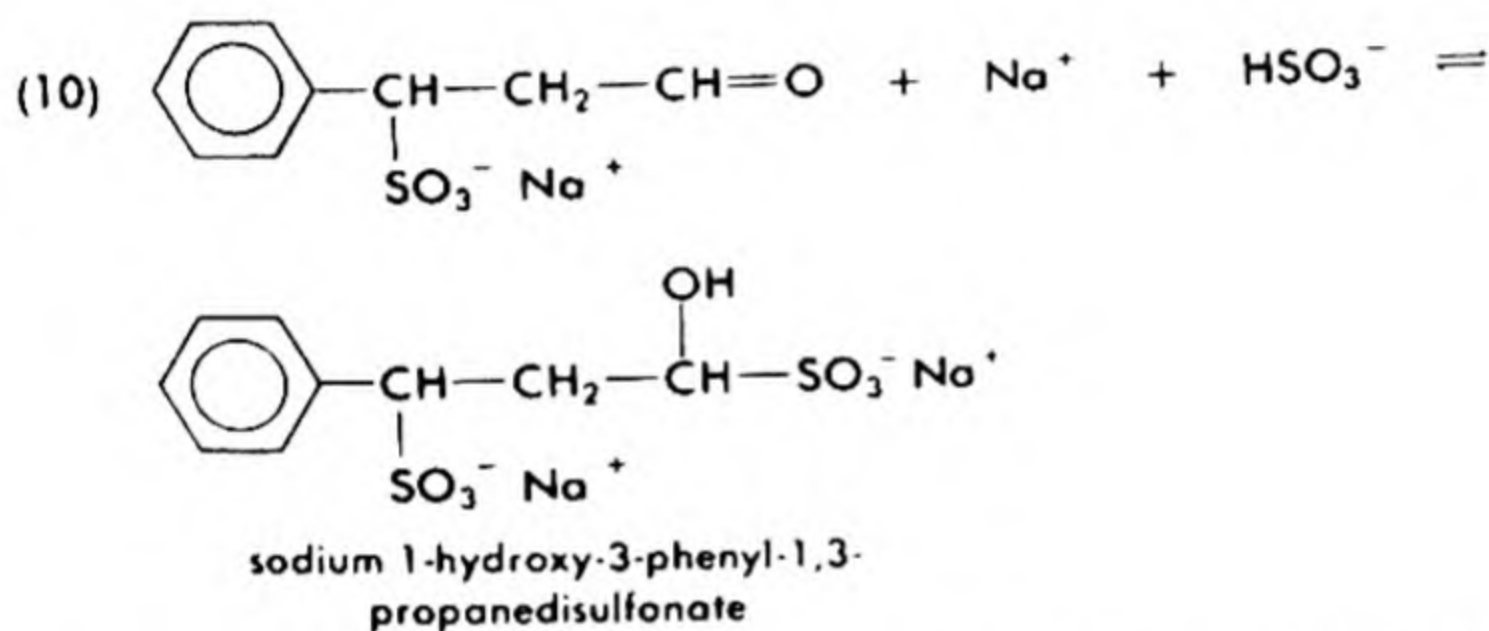
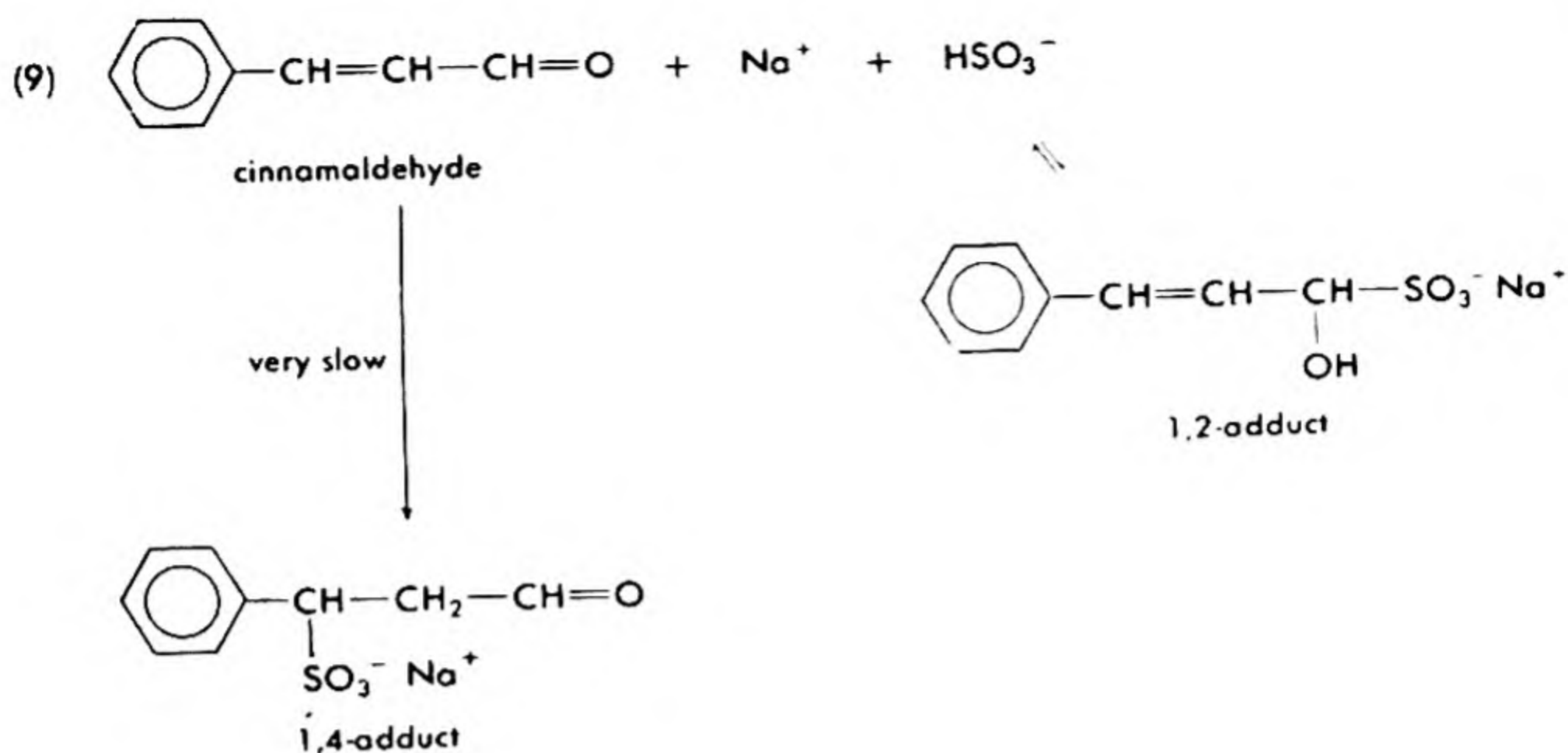


22-3 ADDITIONS TO α,β -UNSATURATED ALDEHYDES, KETONES, AND ESTERS

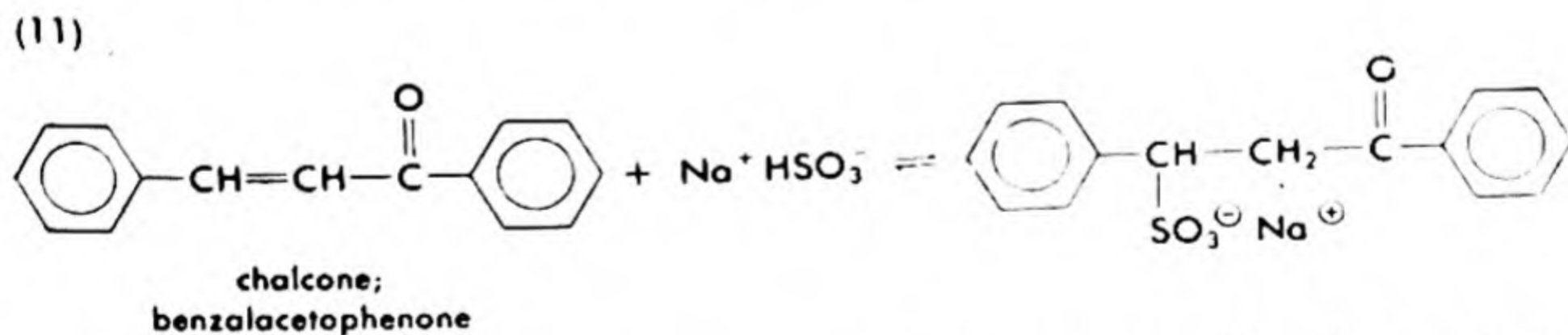
While most aldehydes and some ketones add sodium bisulfite to the carbonyl group (eq. 8) via a nucleophilic process (§18-2E), α,β -unsaturated carbonyl compounds can add this reagent to the carbon-carbon double-



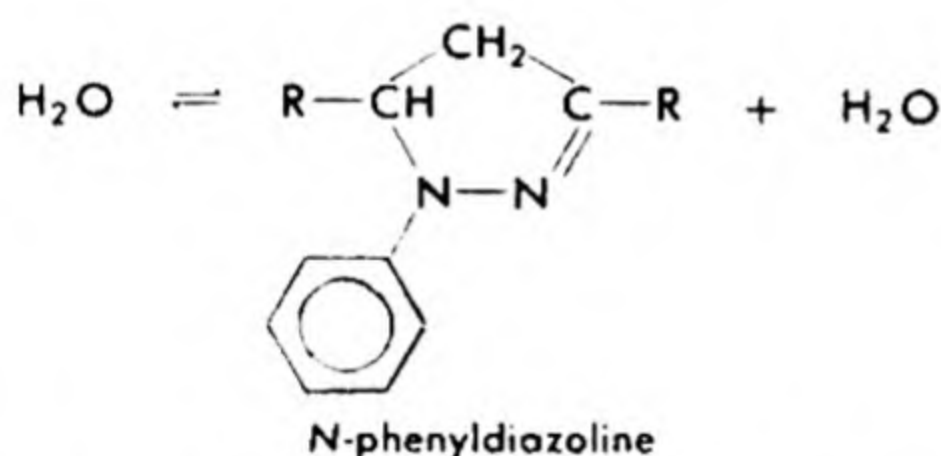
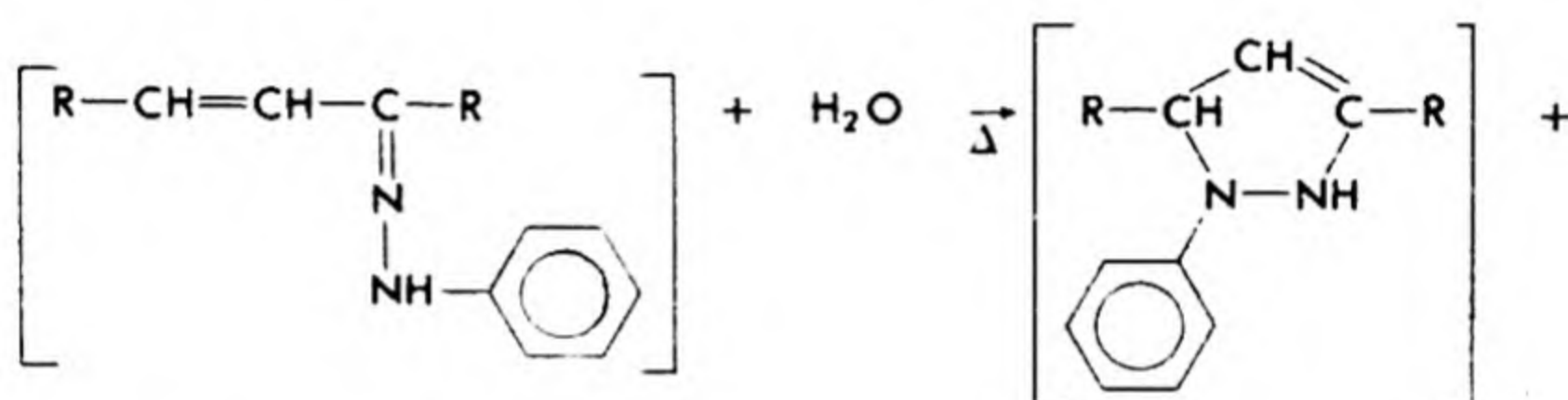
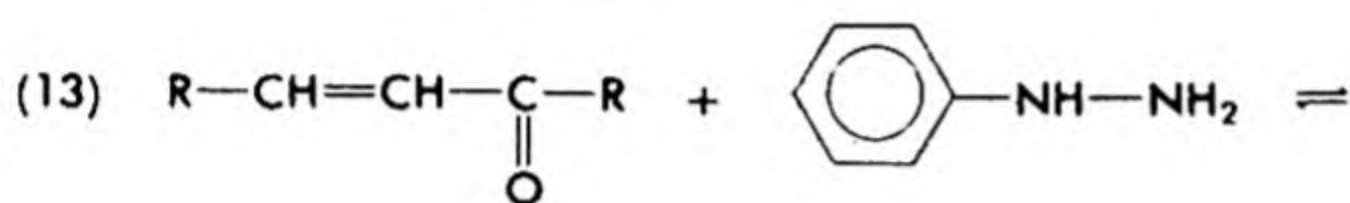
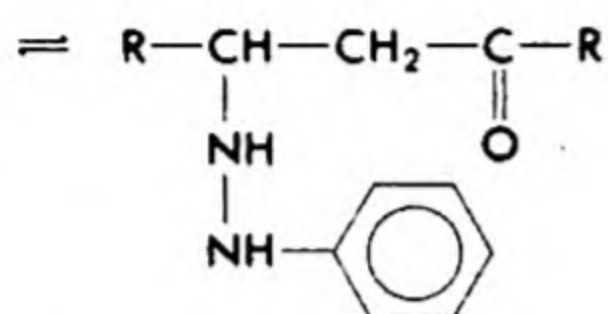
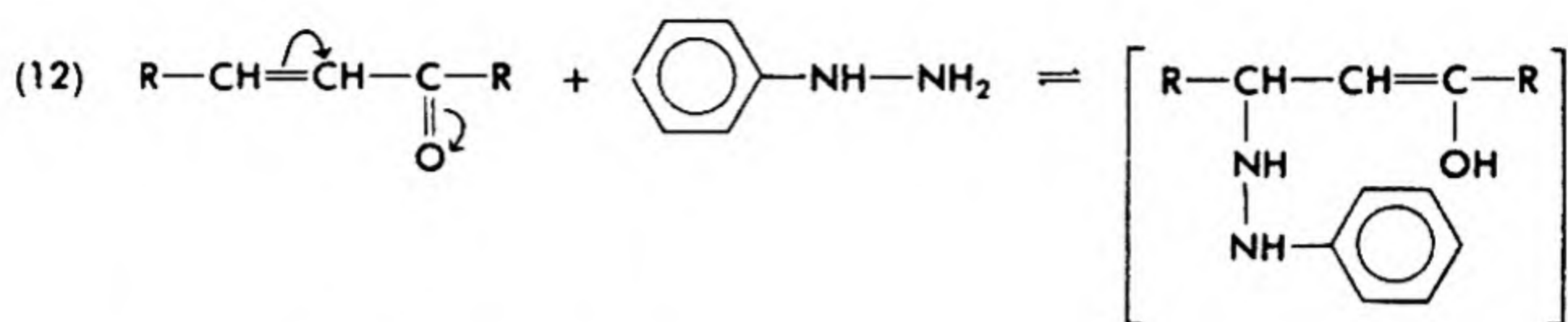
bond system instead after a sufficiently long period of time. Cinnamaldehyde reacts rapidly at the aldehyde group, and more slowly by conjugative (1,4) addition, to give, after a time, an addition product having the groups from 2 moles of the bisulfite. While the 1,2-addition is readily reversed, the 1,4-addition is not.



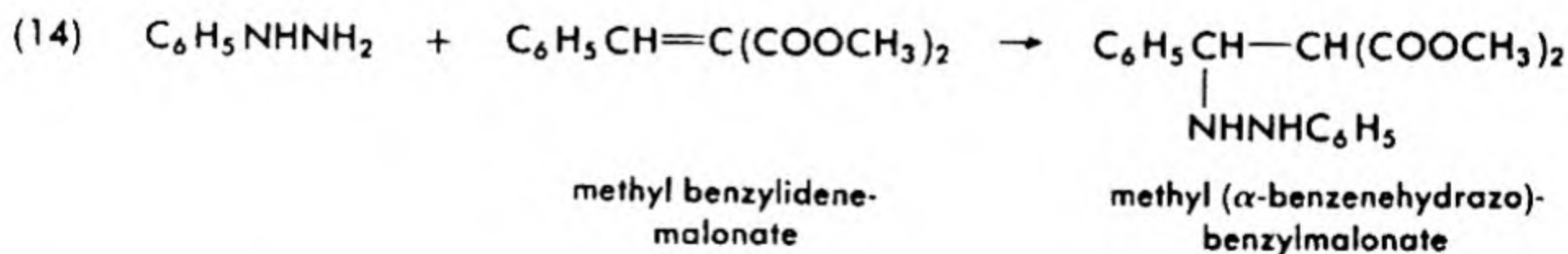
Ketones, on the other hand, often add 1,4 more readily than 1,2, leading to products which contain only 1 mole of sodium bisulfite. Such a reaction is that of benzalacetophenone (eq. 11).



Ammonia, ammonia derivatives, and hydrogen cyanide add similarly. Conjugated unsaturated aldehydes and ketones show competition between 1,2-addition and 1,4-addition, with consequences such as shown in eqs. (12) and (13). All the reactions are reversible. With phenylhydrazine, the diazoline is the most stable product, but usually forms only at higher temperatures.



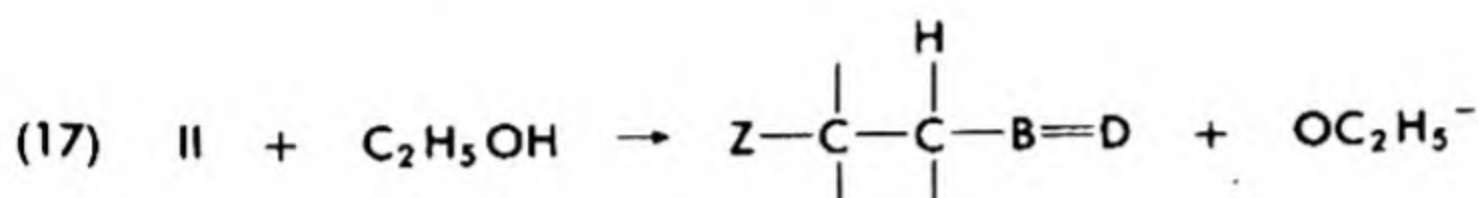
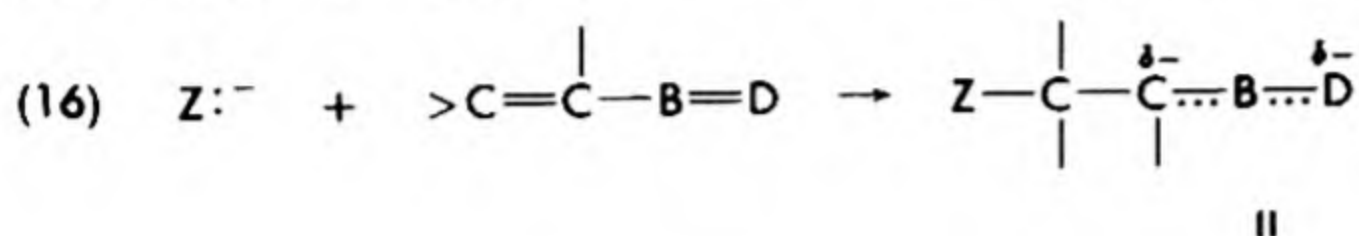
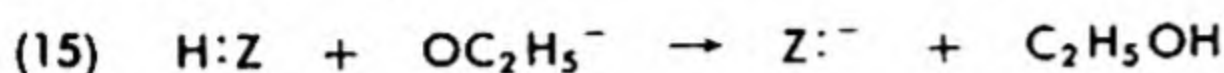
Phenylhydrazine also adds to methyl benzylidenemalonate to give the 1,4-adduct (eq. 14).



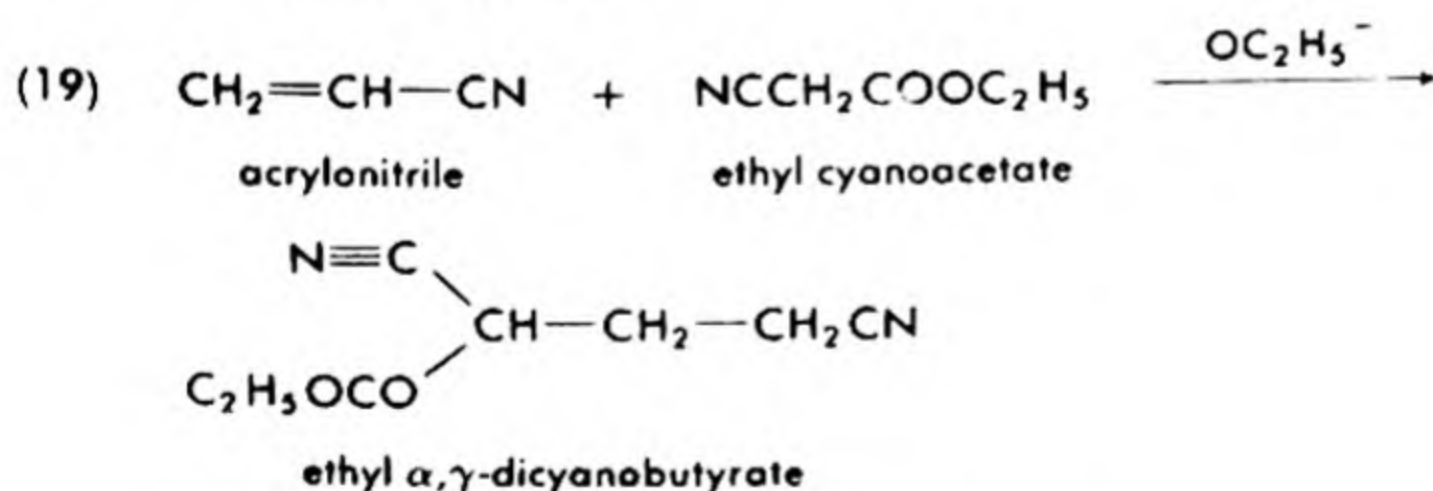
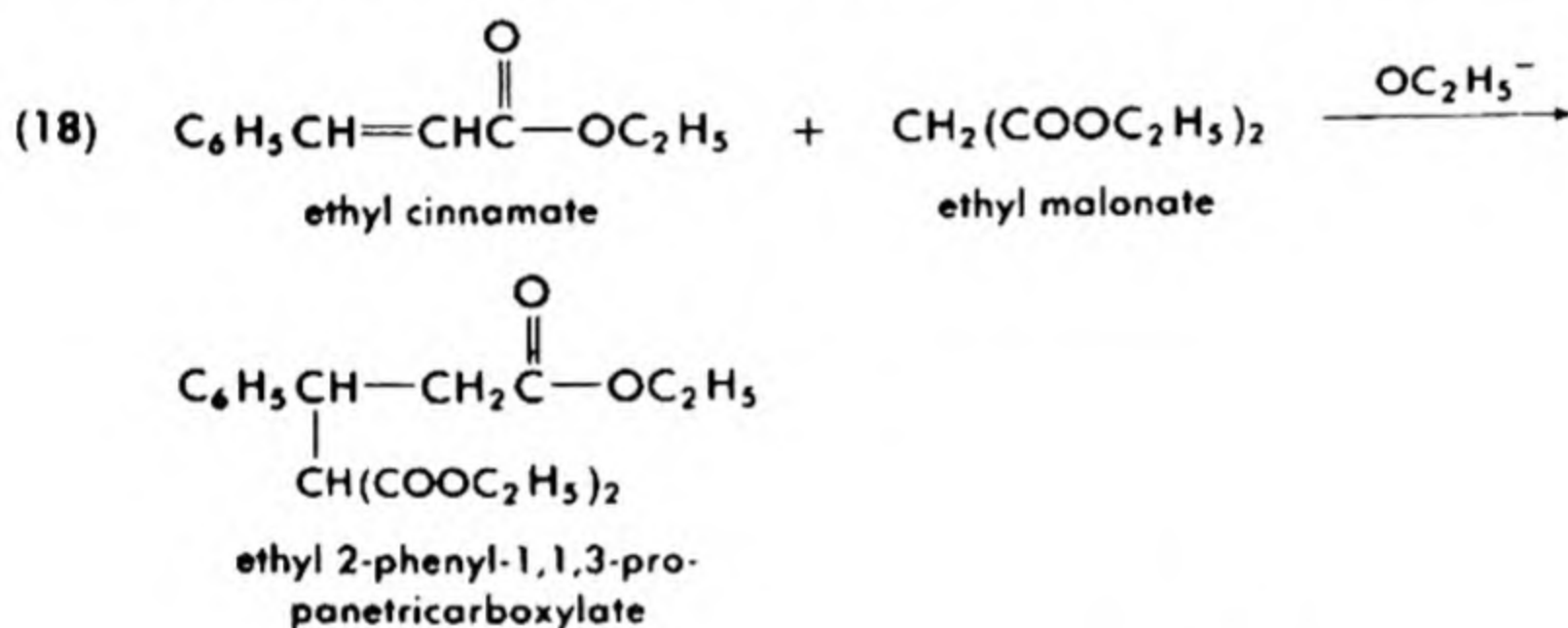
22-4 MICHAEL ADDITION REACTIONS

When a new carbon-carbon bond is produced by nucleophilic addition to conjugated systems, the process is called a *Michael addition*, after the American chemist who discovered the reaction. The process represents a powerful tool for making carbon-carbon bonds. The generalized process involves an α,β-unsaturated compound and a compound containing an

active hydrogen attached to a carbon-atom (e.g., malonic ester, acetoacetic ester, nitro compounds, aldehydes, ketones, etc.). These are condensed in the presence of a base. In the equations that follow, the active hydrogen compounds are described as $H:Z$.

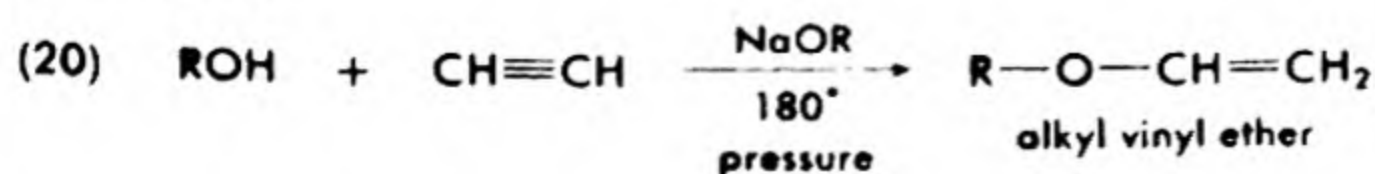


Examples include the condensation of malonic ester with ethyl cinnamate (eq. 18) and ethyl cyanoacetate with acrylonitrile (eq. 19).

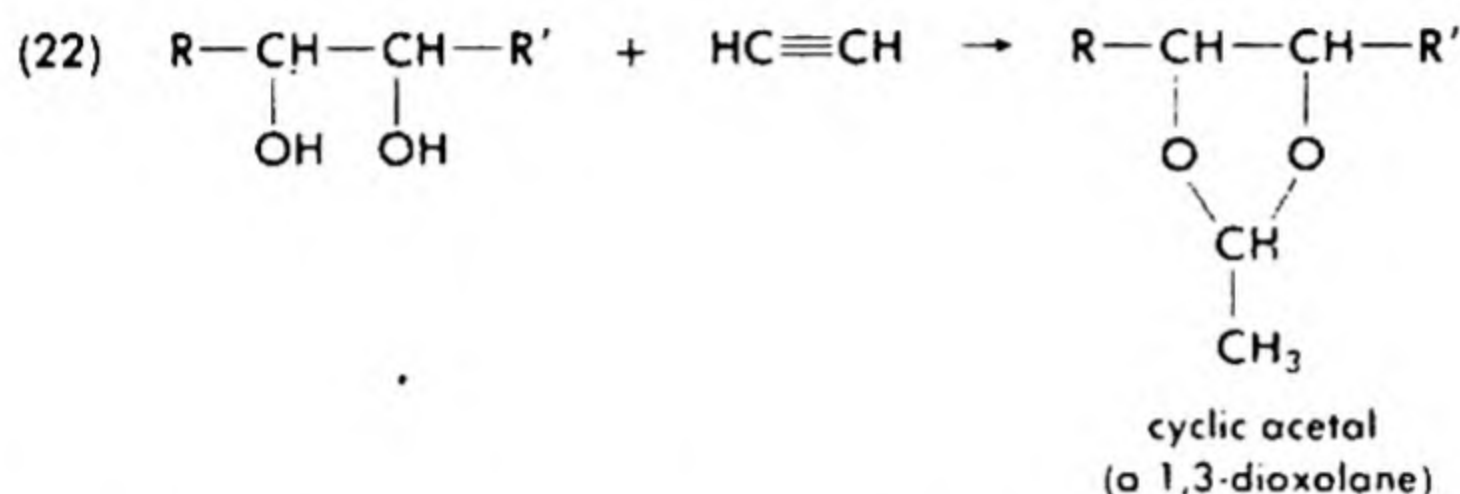
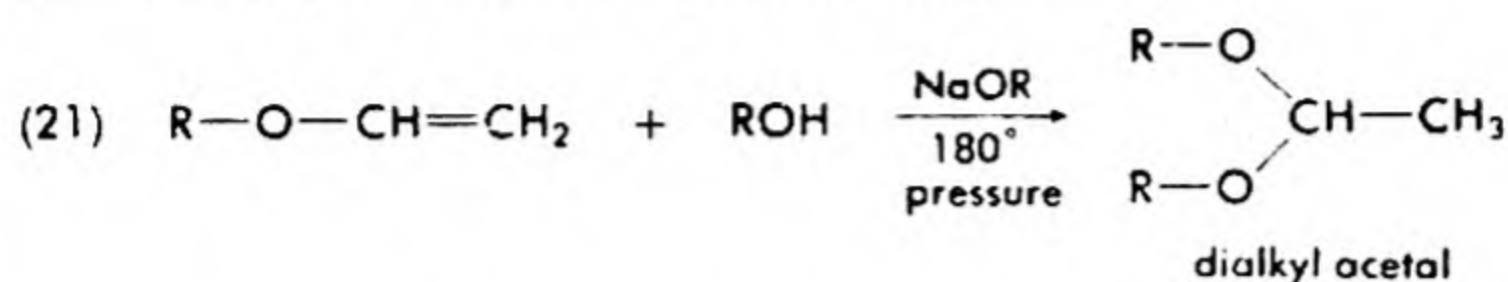


22-5 ADDITIONS TO ACETYLENES. VINYLATION

While alcohols do not add to olefins in the presence of bases, acetylene undergoes nucleophilic addition of alcohols in the presence of alkoxides to give alkyl vinyl ethers. The reactions require elevated temperatures and pressures.

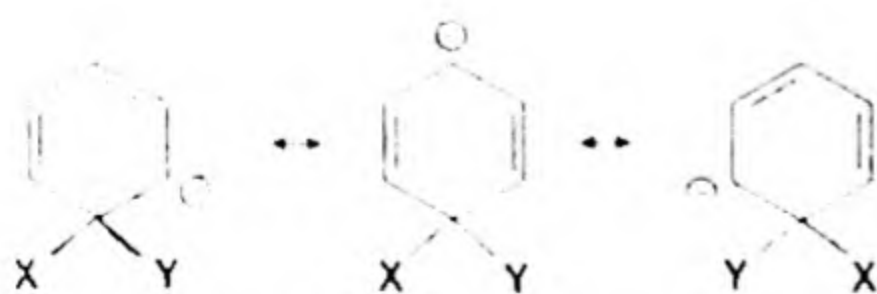
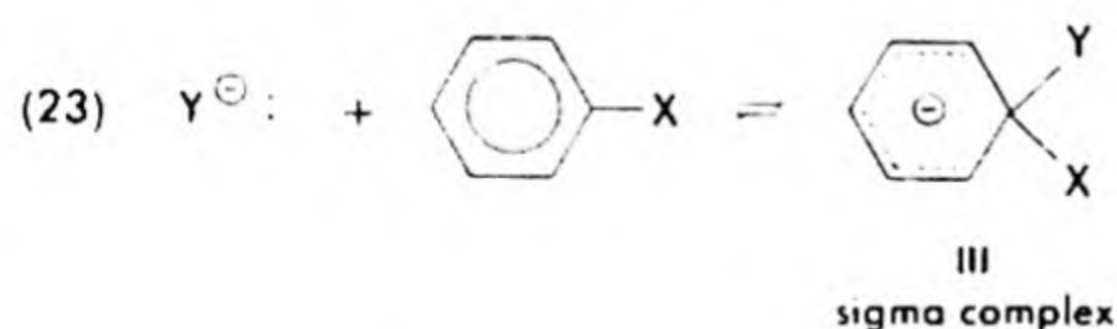


A side reaction is formation of acetals (eq. 21). When cyclization is possible (eq. 22), this is especially important.

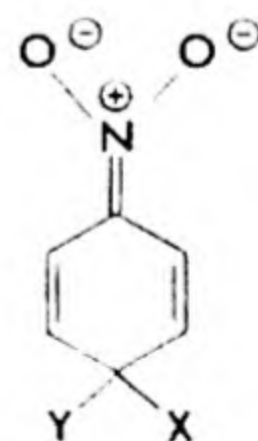


22-6 AROMATIC NUCLEOPHILIC DISPLACEMENTS

Displacements on aromatic rings by nucleophiles can proceed by mechanisms involving the *addition-elimination* type such as those described above for carbonyl compounds. The generalized mechanism for such reactions is described in eq. (23) where the sigma complex intermediate may be considered as a hybrid of structures given below. It now appears unlikely that such a mechanism ordinarily obtains with unactivated benzene rings (see below), but it is reasonable that such a mech-



valence-bond structures of sigma complex

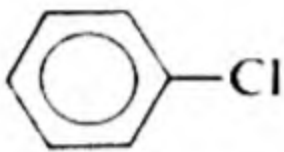
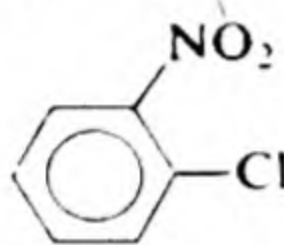
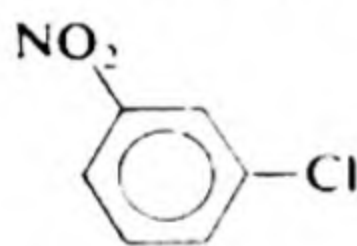
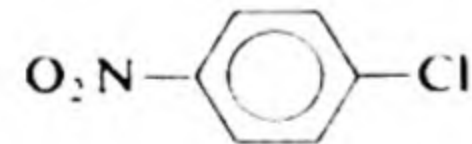
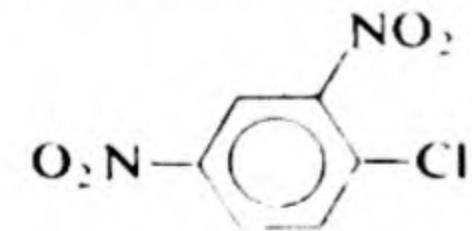
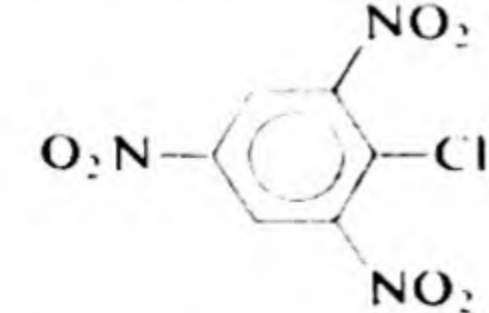


extra valence-bond structure
for *para* activation

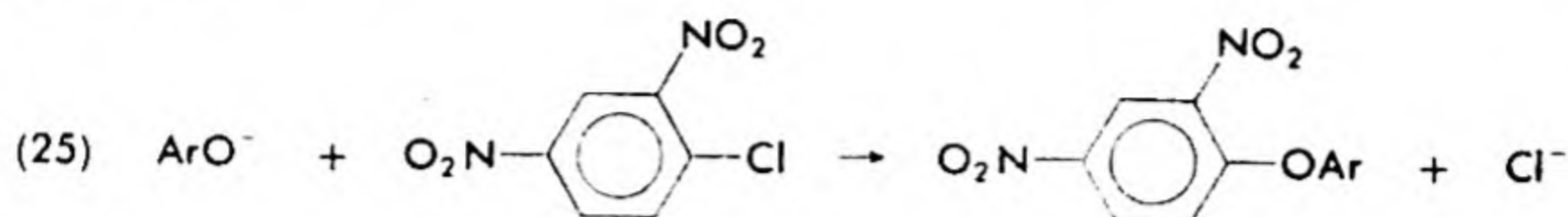
anism will be promoted by the presence of electron-attracting atoms or groups on the ArX molecule, in particular when they are located on *ortho*

and *para* positions relative to the X group being displaced. For example, a *para* nitro substituent has an extra valence-bond structure contributing to the stabilization of the intermediate and therefore to the transition state leading to it. Reactivity is thereby increased. The effects of nitro substitution on the basic hydrolysis of chlorobenzene is shown in Table 22-1. Thus, reactivity varies from that of inert chlorobenzene, on the one hand, which is insensitive to sodium hydroxide in refluxing alcohol and requires

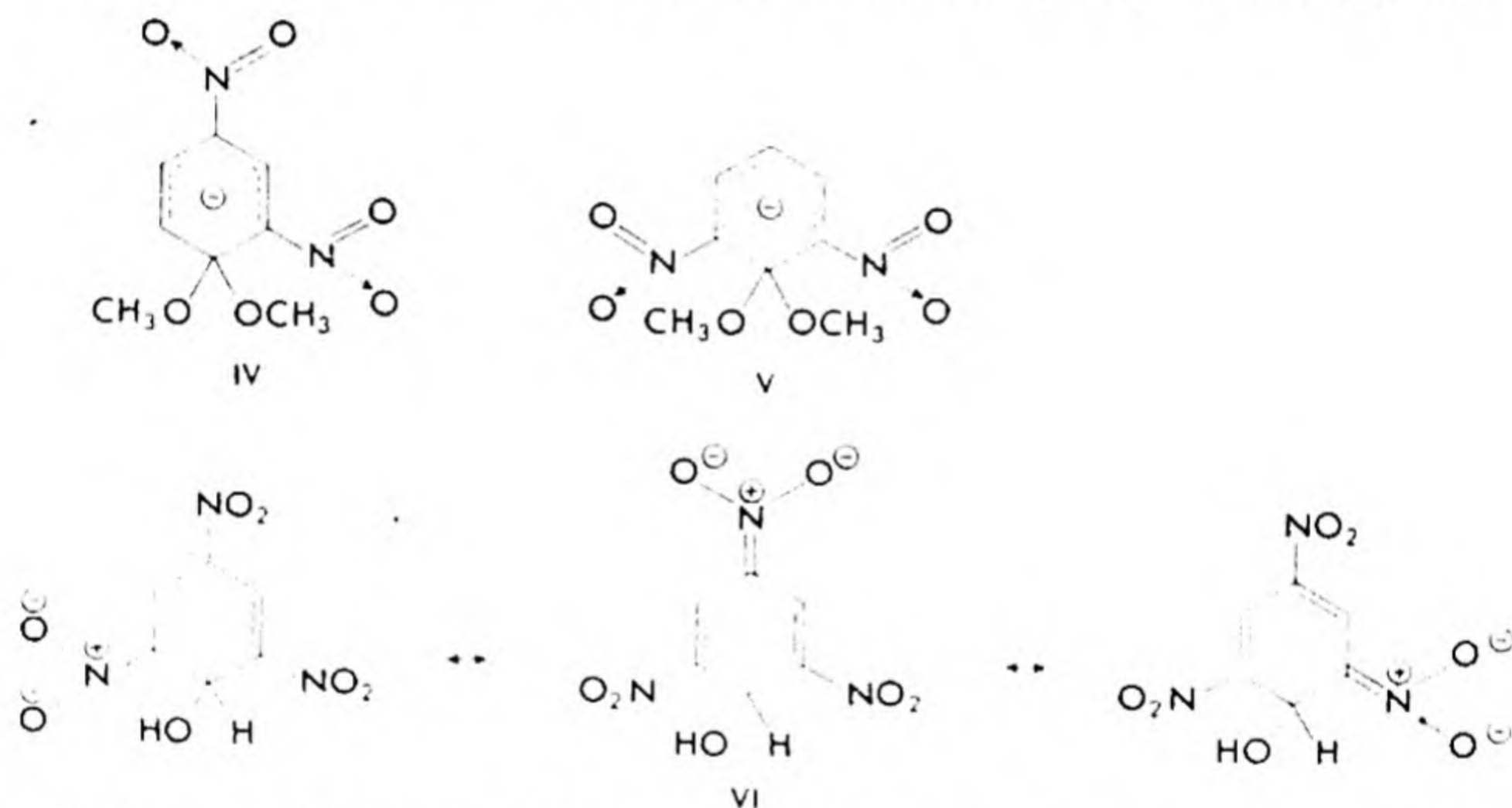
TABLE 22-1. Temperatures Required To Convert Substituted Chlorobenzenes To the Corresponding Phenols Upon Treatment with Sodium Hydroxide.

Compound	Temperature for Conversion, °C
 chlorobenzene	350
 <i>o</i> -nitrochlorobenzene	130
 <i>m</i> -nitrochlorobenzene	does not proceed at 130
 <i>p</i> -nitrochlorobenzene	130
 2,4-dinitrochlorobenzene	80
 2,4,6-trinitrochlorobenzene picryl chloride	25

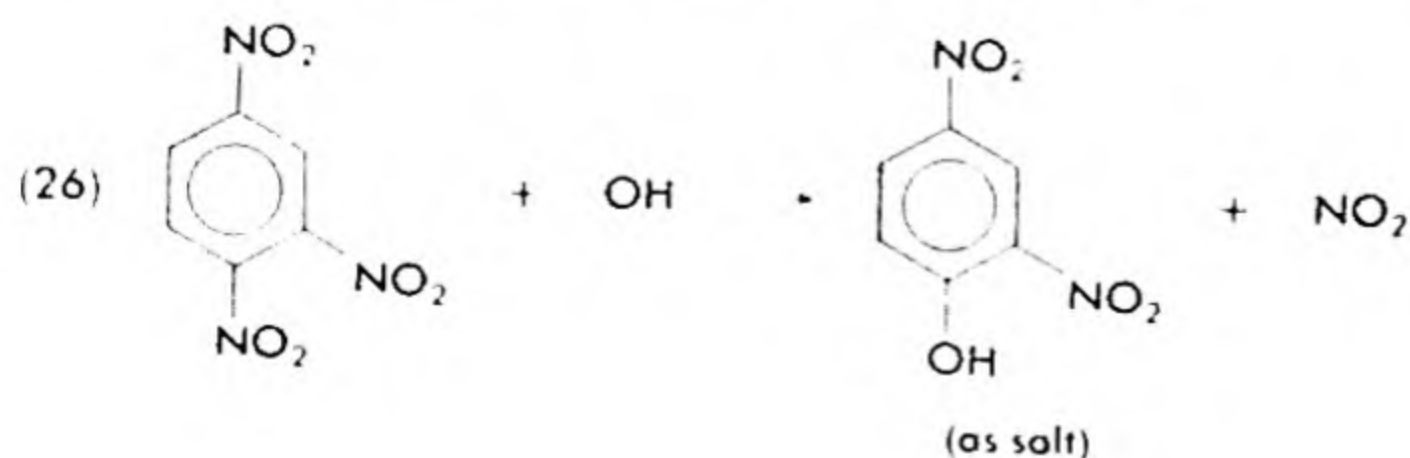
Dow process conditions (§7-3A(4)) to give phenol, to that of picryl chloride, which has the reactivity of a typical acid chloride. 2,4-Dinitrochlorobenzene is utilized as a reagent for the characterization of phenols (eq. 25).



Again evidence is good that a sigma complex intermediate intervenes in suitably activated systems. For example, addition of 2,4-dinitroanisole or 2,6-dinitroanisole to a solution of sodium methoxide in methanol gives brilliantly colored solutions. These colors are ascribed to the presence of IV and V, respectively (resonance hybrids). Colored species are also observed with *m*-dinitrobenzene (but not *ortho* or *para*) in strongly basic

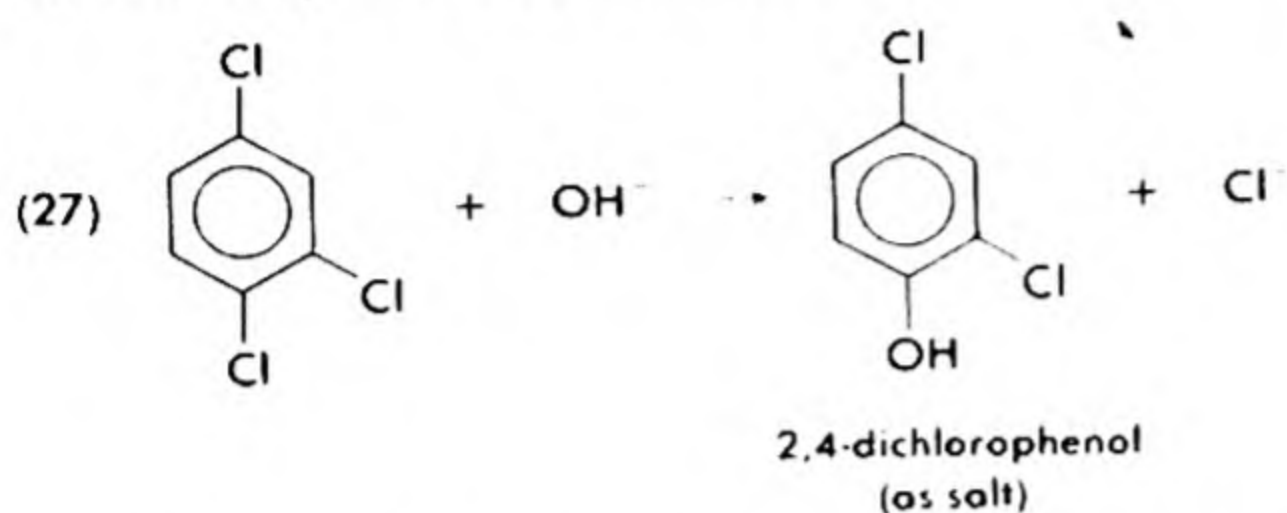


solution. 1,3,5-Trinitrobenzene and TNT are indicators, developing colors at about pH 13-14 (VI). All of these reactions involve the addition of nucleophiles to the aromatic system to form the highly delocalized anionic products. Consideration of canonical structures makes it clear that only nitro groups in positions *ortho* and *para* to the entering nucleophile can be effective by conjugation, and also that nitro groups should be *meta* to each other for an efficient indicator.

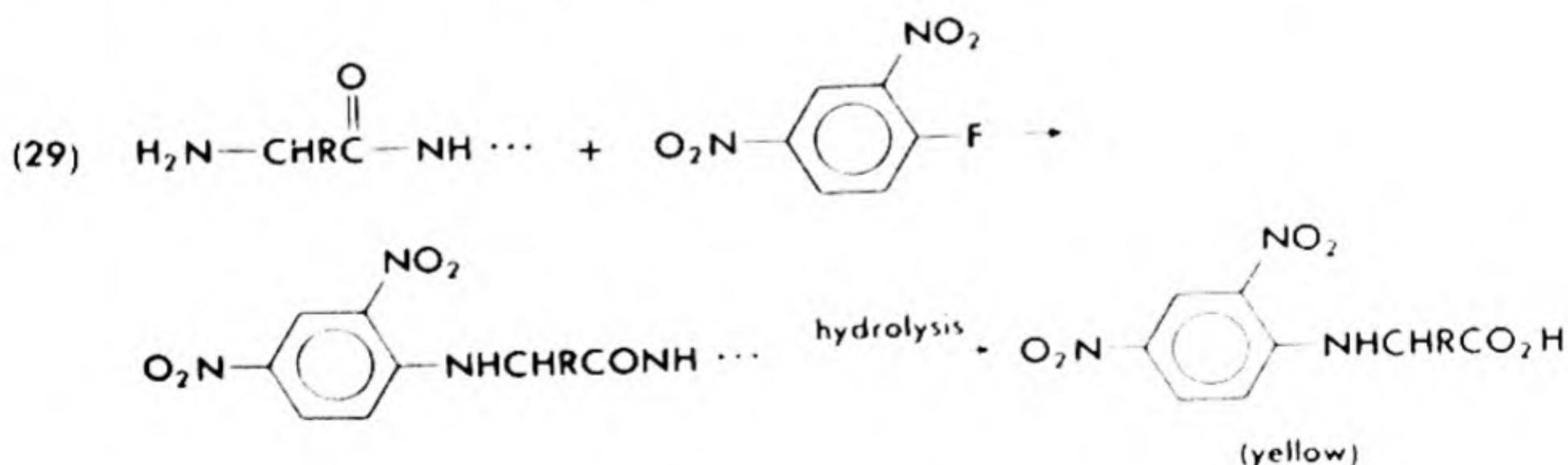
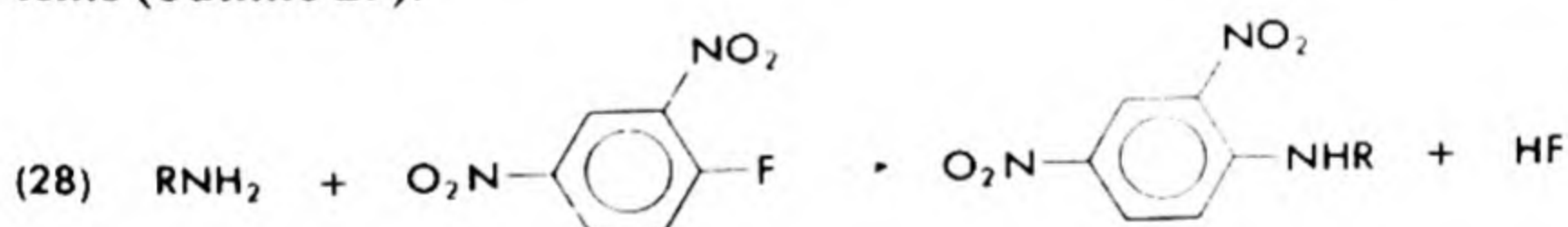


Halogen can be readily displaced from nitrochloroarenes, and certain nitro groups also undergo ready displacement (eq. 26).

Other electron-attracting groups have similar, if less dramatic, effects on reactivity. The preparation of 2,4-dichlorophenol, which is the key intermediate in the preparation of the herbicide, 2,4-D (see §42-2B), is another example of such a reaction.



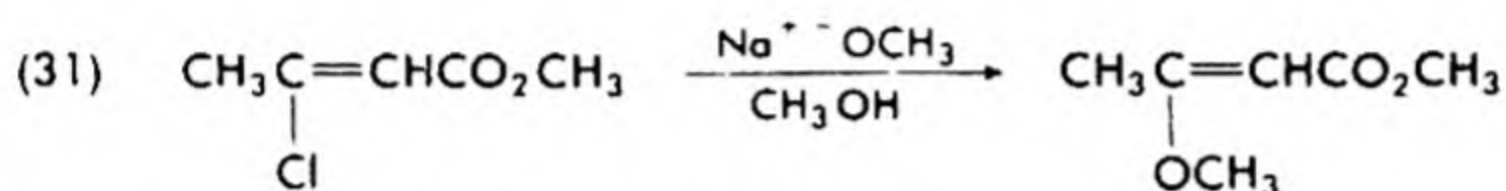
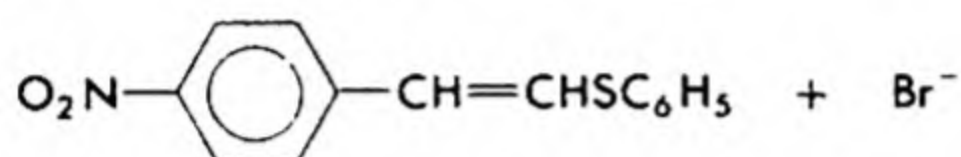
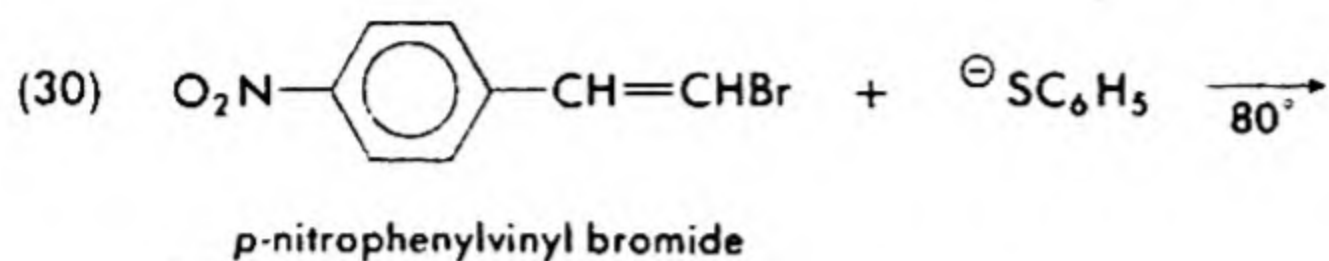
As the step represented by eq. (23) is rate-determining and as this step does not involve breaking of the arene-X bond, reactivities of aryl halides do not necessarily parallel those of alkyl halides. In fact, the reactivities do not necessarily parallel those of alkyl halides. In fact, the reactivities reflect electronegativity rather than polarizability; consequently, 2,4-dinitrofluorobenzene is substantially more reactive than the corresponding chloride. It is used as a reagent for amines (eq. 28) and, in particular, to identify the terminal group in polypeptide fragments from the partial hydrolysis of proteins in the analysis of the order of amino acids in proteins (outline 29).



22-7 NUCLEOPHILIC DISPLACEMENTS IN VINYL HALIDES

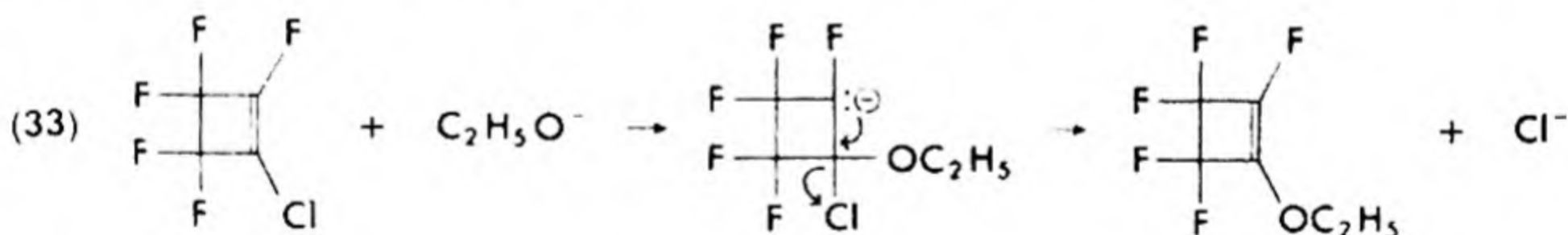
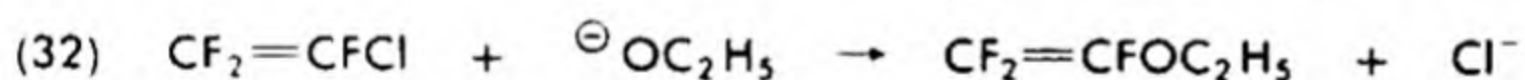
Unactivated vinyl halides, like aromatic halides, do not undergo direct displacement or carbonium ion displacements readily (see §12-1B(4)). Here again, however, suitable activating groups facilitate displacement via the addition-elimination mechanism. Thus, for example, *p*-nitrophenylvinyl

bromide undergoes ready displacement by mercaptide ions (eq. 30), whereas vinyl bromide is inert under the same conditions. Similar results



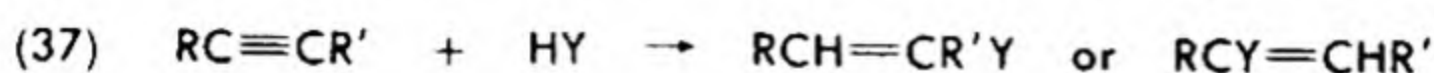
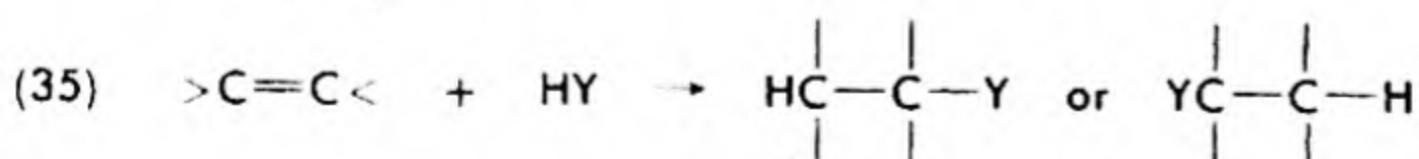
methyl β -chlorocrotonate

are observed with methyl β -chlorocrotonate and methoxide ion (outline 31). In each case an intermediate with the negative charge delocalized into the nitrophenyl group (eq. 30) or into the carbonyl group (outline 31) can be written. Fluorine atoms, being strongly electronegative, readily stabilize negative charges, so that displacements of polyfluorovinyl halides by bases such as alkoxides go readily, even at 80° (eqs. 32 and 33).



22-8 AROMATIC NUCLEOPHILIC DISPLACEMENTS VIA ARYNE INTERMEDIATES. ELIMINATION-ADDITION MECHANISMS

Still another process by which a net displacement can occur involves an elimination reaction followed by an addition reaction, as outlined in eqs. (34) and (35) or (36) and (37). Such processes might be anticipated when



(a) the system is one in which elimination and nucleophilic addition to the multiply bonded system occur with ease or (b) the system is one in which

the more usual mechanisms for displacement are only difficultly available. Diagnosis of such mechanisms is sometimes difficult as the reaction has the same kinetics as the direct-displacement process or the addition-elimination process (eq. 38) so that measurement of kinetic order is of no help. The *elimination-addition mechanism* can be definitely excluded when

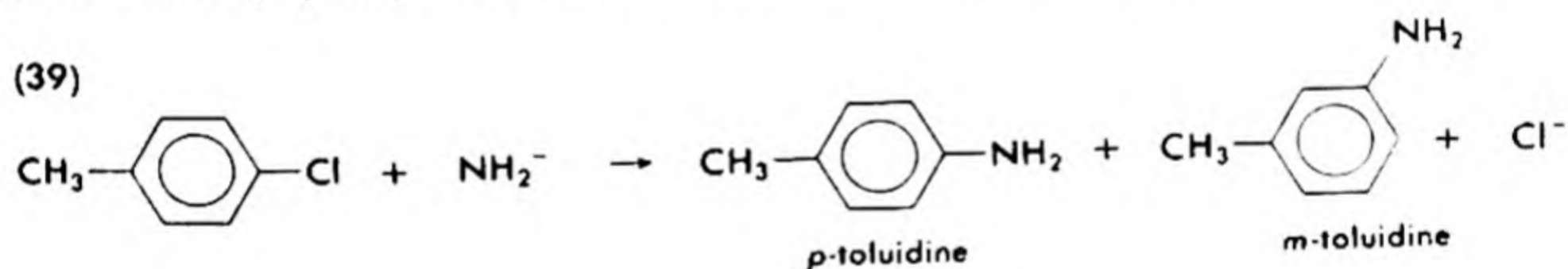
$$(38) \quad \text{rate} = k(\text{RX})(\text{Y})$$

the addition reactions (eqs. 35 or 37), can be studied separately, if they are observed to proceed at rates slower than those observed for the overall displacement reaction. When this is not the case, this mechanism must always be considered as a possibility.

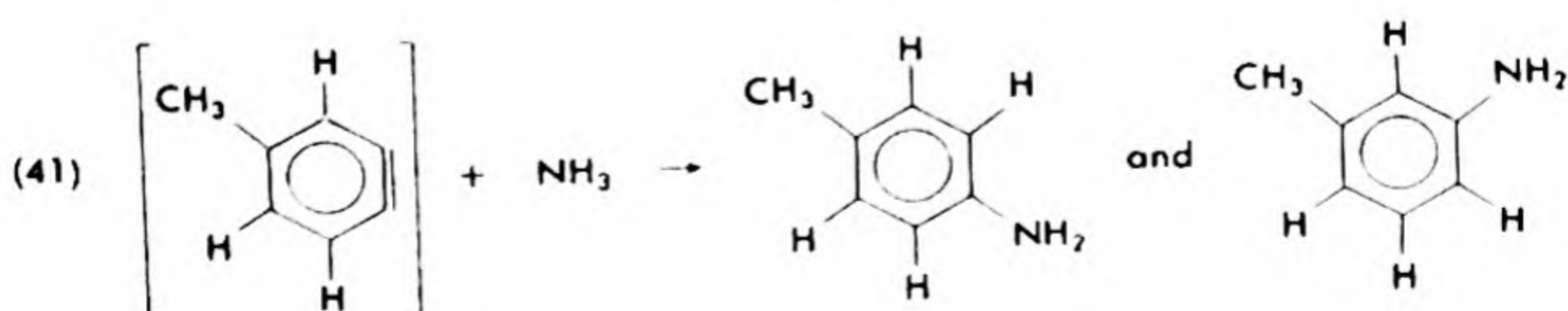
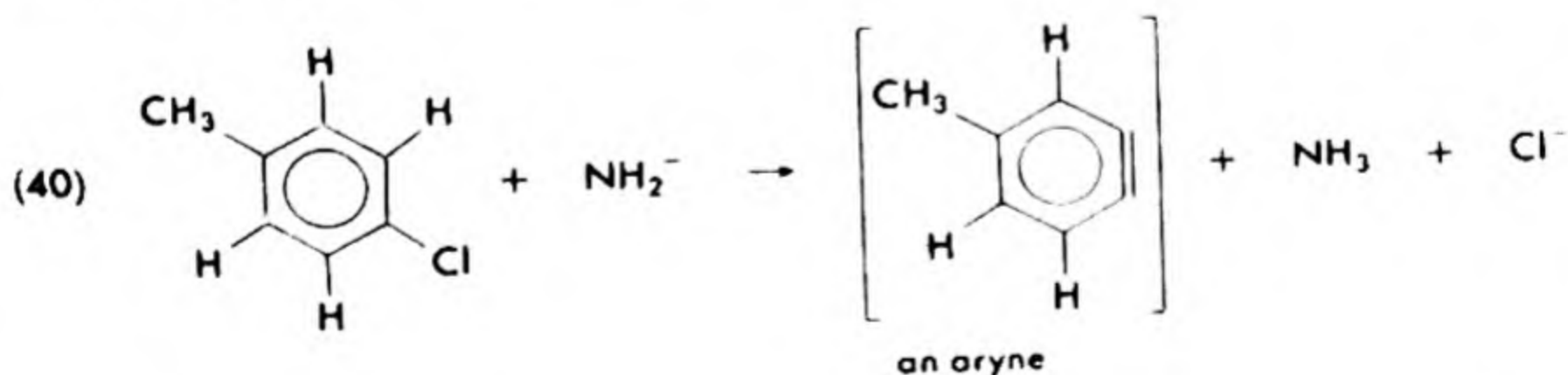
A certain diagnosis for this mechanism may be made when rearrangement occurs. Careful scrutiny of eqs. (35) and (37) indicates that HY may add to the multiple bond either in the direction of the original HX removal or in the opposite direction. When the latter occurs, elimination-addition is demonstrated.

A. The Aryne Problem

As has been noted, displacements on unactivated benzene rings, say in chlorobenzene, by hydroxide ion or by amide ion, require drastic conditions. It was observed that treatment of *p*-chlorotoluene with sodamide gave not pure *p*-toluidine, as expected, but instead a mixture of *m*- and *p*-toluidine (eq. 39). This rearrangement seems best explained by the as-



sumption that a reactive intermediate called an *aryne* is involved (eq. 40 and outline 41).



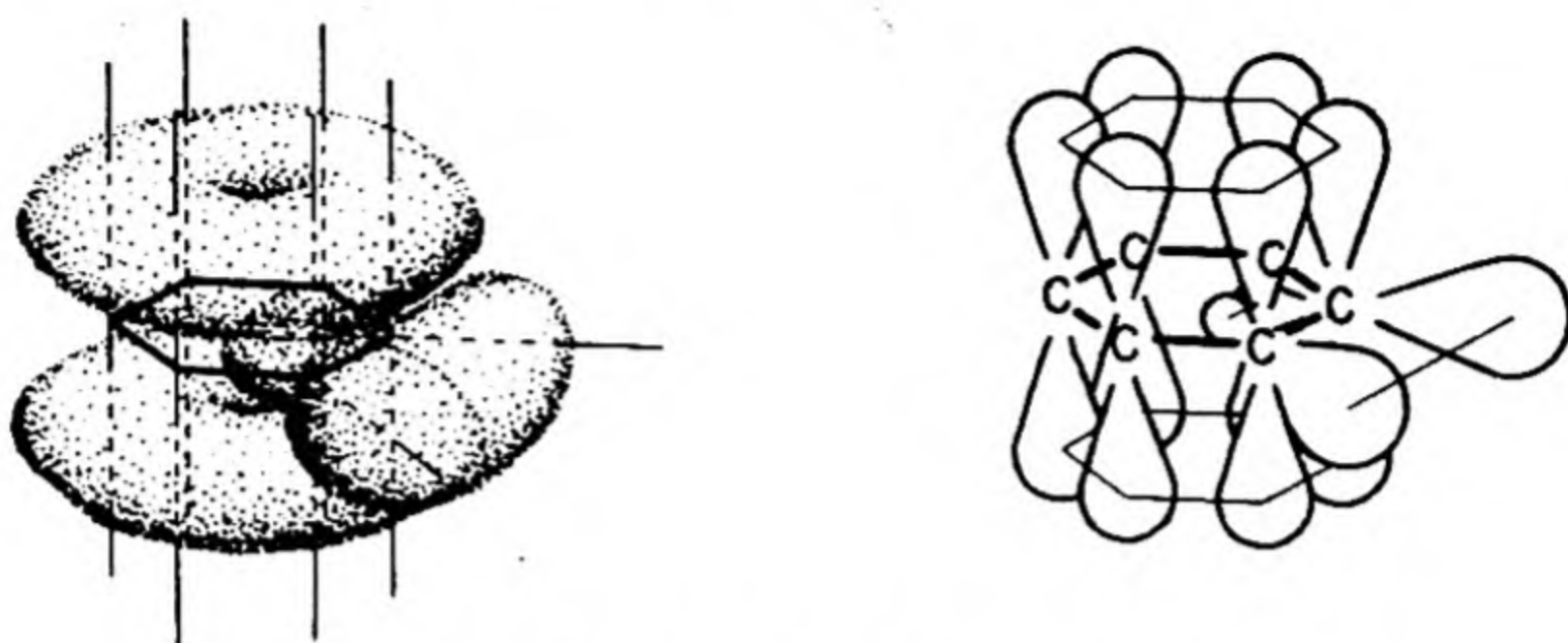
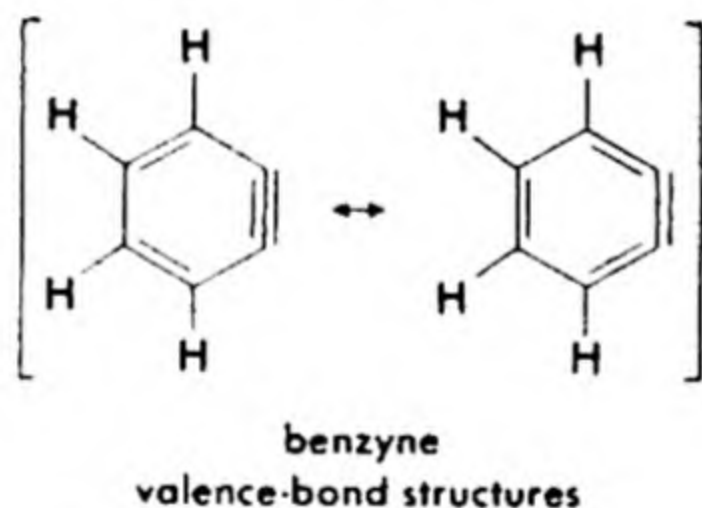
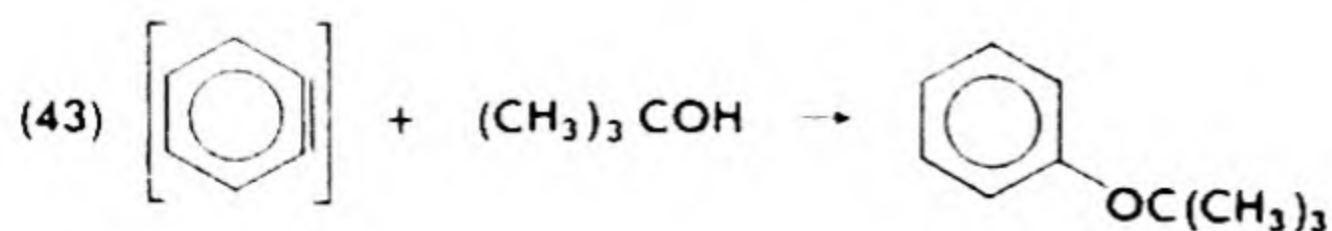
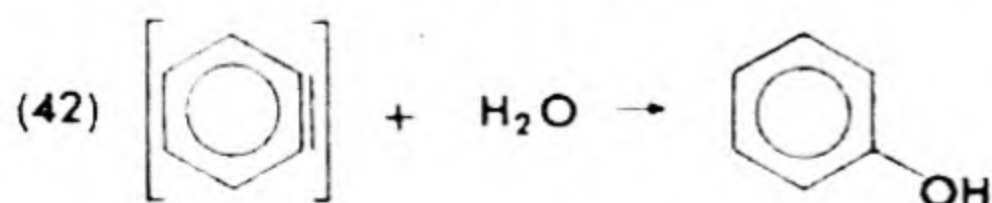


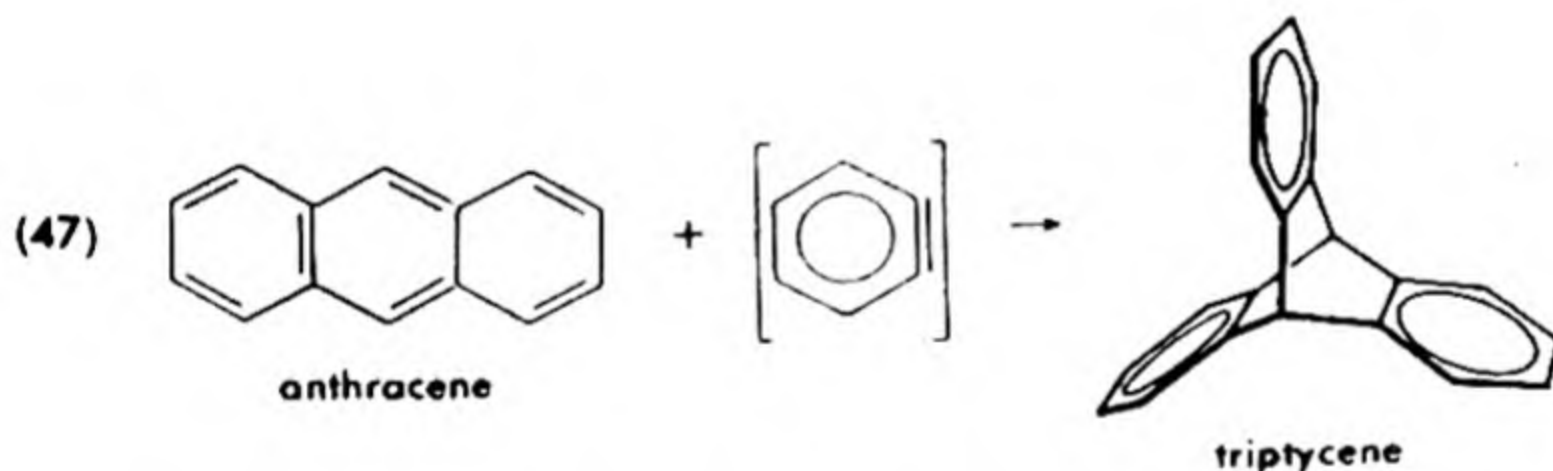
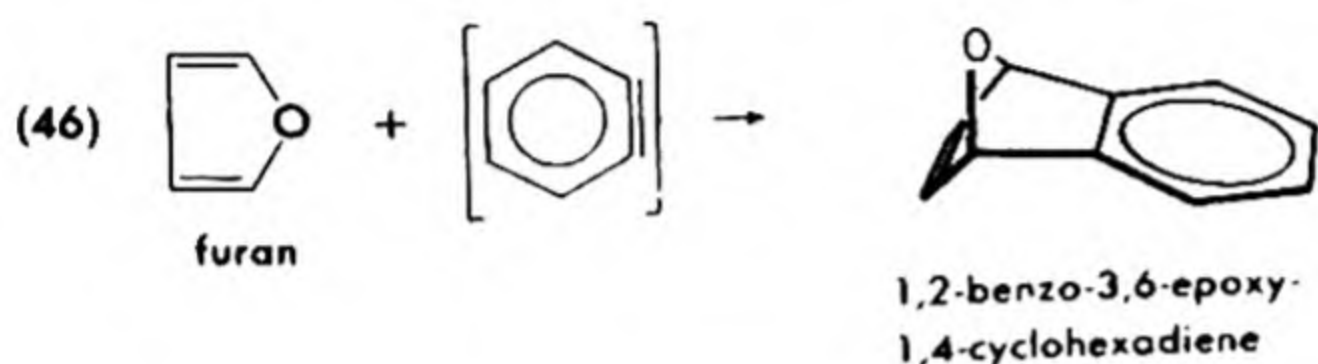
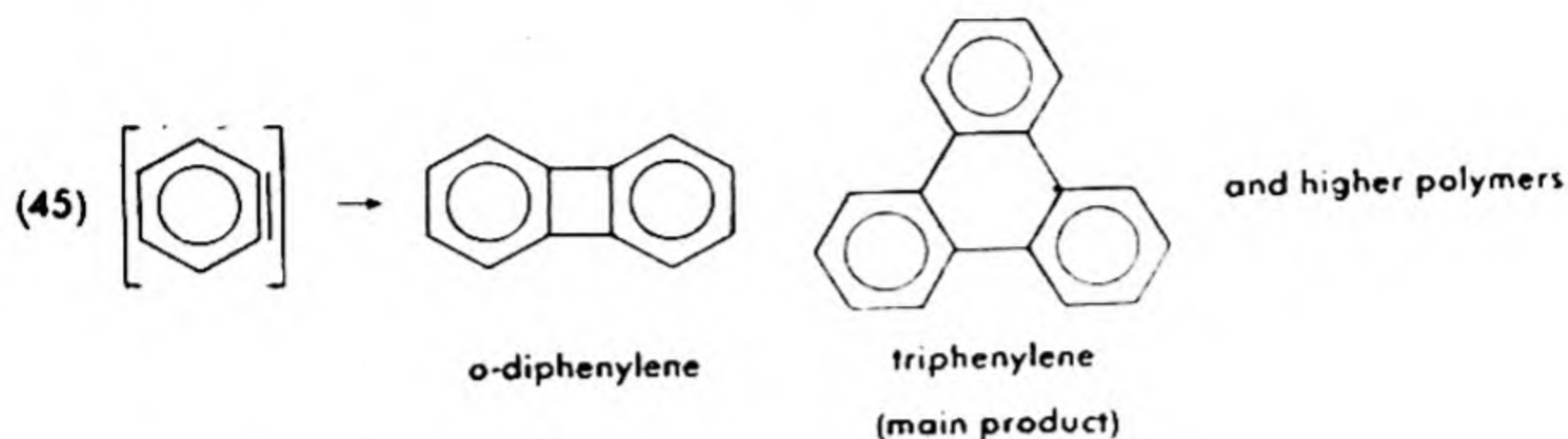
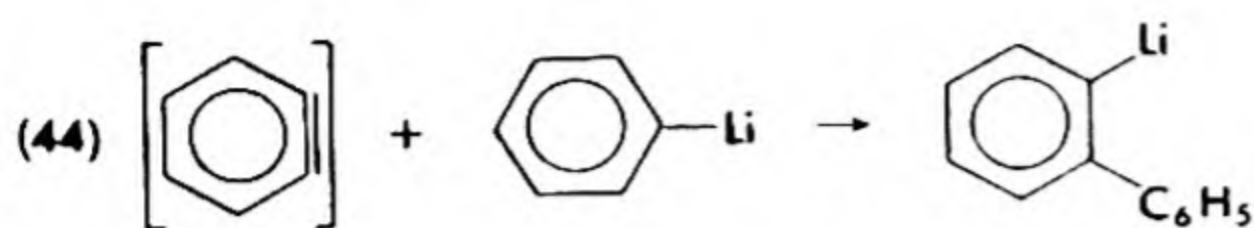
Fig. 22-1. MO Cloud and MO Diagram for Benzyne.

Such intermediates, of which the parent member is *benzyne* (below and Fig. 22-1) have been observed in a variety of reactions. One sees that besides the π system of six delocalized electrons, there is a pair of electrons localized on the two carbon atoms (Fig. 22-1). The orbitals containing these electrons are perpendicular to the π system and are therefore unable to interact favorably with it. These orbitals have an angle of 60° with each other, so that little delocalization stabilization is available from

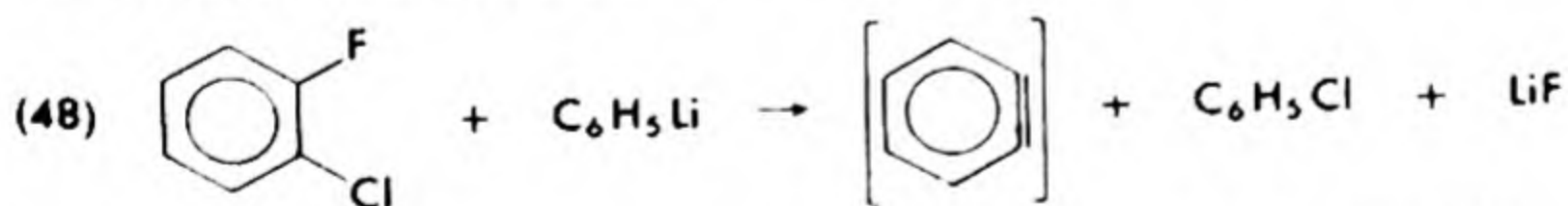


overlap with each other. The σ orbital systems are at 120° rather than the 180° preferred by divalent carbon atoms. The systems may be considered as related to a bent acetylene in which the second of the π orbitals is relatively unstable and therefore especially prone to reactions. Benzyne is in fact quite unstable; it adds many substances, including ammonia (eq. 41), water (eq. 42), alcohols (eq. 43), and phenyllithium (eq. 44). In the absence of suitable reagents, benzyne polymerizes (outline 45). Additional proof of its existence comes from its being trapped by dienes in Diels-Alder reactions (eqs. 46 and 47) and observations of its spectra.





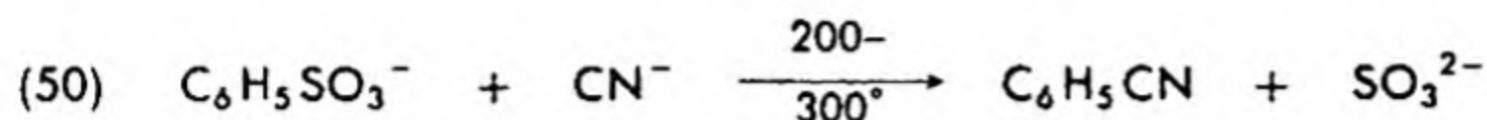
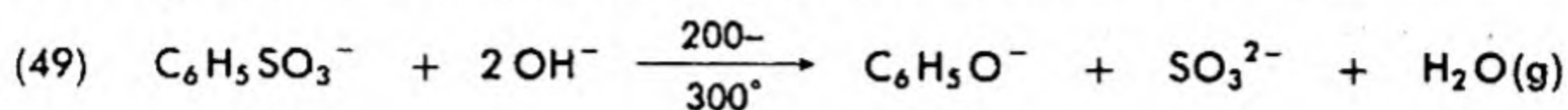
Benzyne (and its analogs) can be readily prepared by the action of phenyllithium with *o*-chlorofluorobenzene (eq. 48). The hydrolysis of chlorobenzene to sodium phenoxide by sodium hydroxide at 350° may go via benzyne. Potassium *tert*-butoxide in dimethyl sulfoxide, which is



many millions times a stronger base than sodium hydroxide (see §10-2C), converts halobenzenes to benzyne and thus to *tert*-butyl phenyl ether (eq. 43) even at room temperature in a few days.

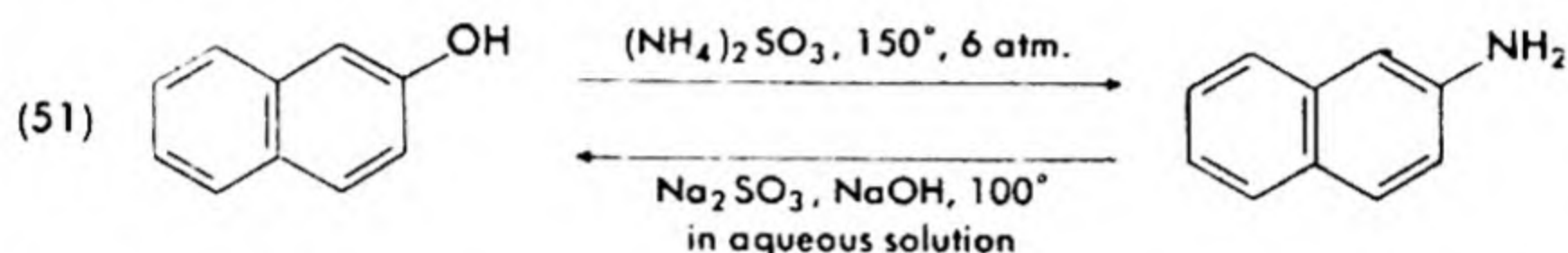
It may be noted that several displacements on simple aromatic systems occur with relative ease and lack of isomerization which appear surprising on the basis of the above discussion. Unfortunately, insufficient evidence is available at present to propose complete mechanisms. The transformations discussed here have general synthetic usefulness, both industrially and in the laboratory.

Arenesulfonate salts are converted to phenols by fusion with a strongly basic hydroxide and to nitriles by fusion with sodium cyanide. The reac-

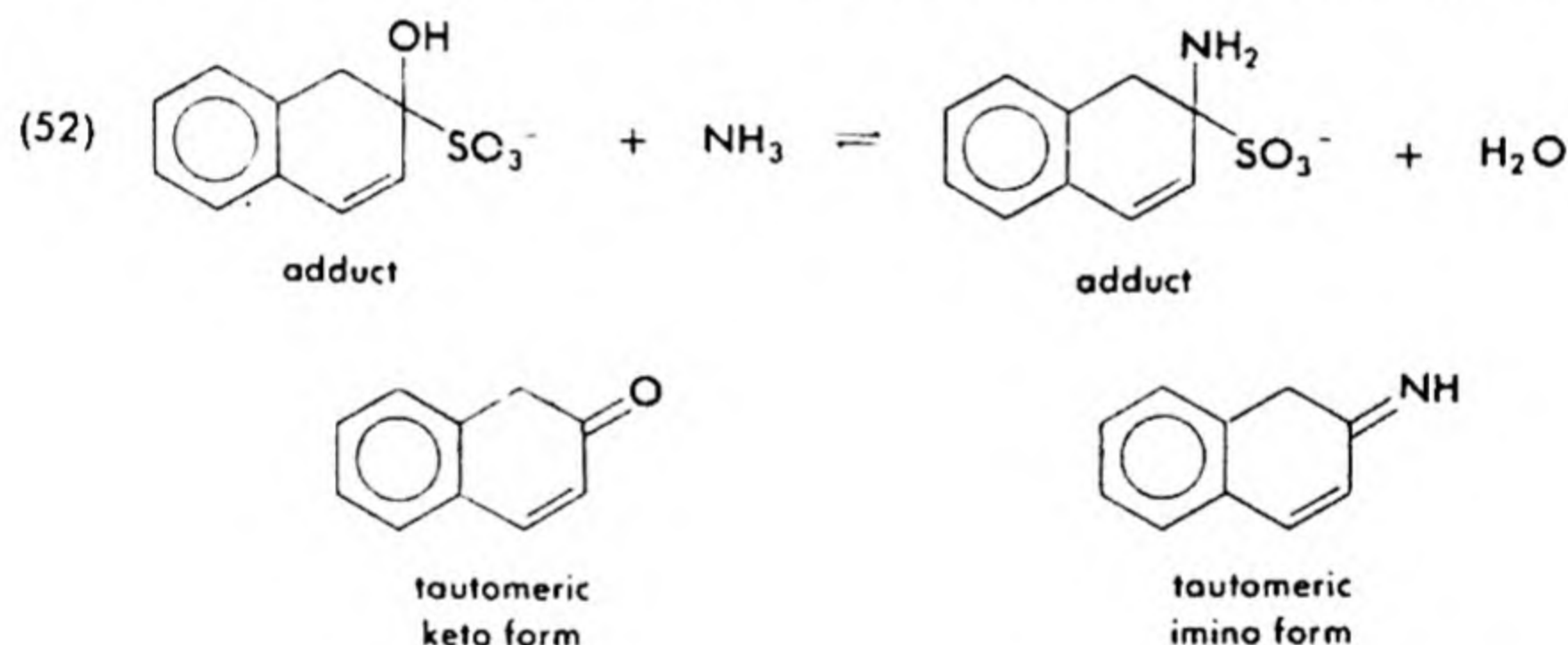


tion is applicable to substituted benzenesulfonates and polynuclear arenesulfonates. One of the oldest industrial syntheses of phenol utilizes this reaction (eq. 49).

β -Naphthols and β -naphthylamines are interconverted in the presence of sulfite ion (the Bucherer reaction).



In this reaction, an adduct of the tautomeric keto or imino form can



sometimes be isolated. It would appear, therefore, that the reaction pathway may involve a reversible addition-elimination of bisulfite ion similar to participation by cyanide ion in the benzoin condensation (§23-4).

SUPPLEMENTARY READINGS

- Gould, E. S., *Mechanism and Structure in Organic Chemistry*, Holt-Dryden, New York, 1959, pp. 452-456, 460-464, 527-529.
 Heaney, H., "The Benzyne and Related Intermediates," *Chem. Rev.*, **62**, 81-97 (1962).
 Hine, J., *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, New York, 1962, Chapter 17.

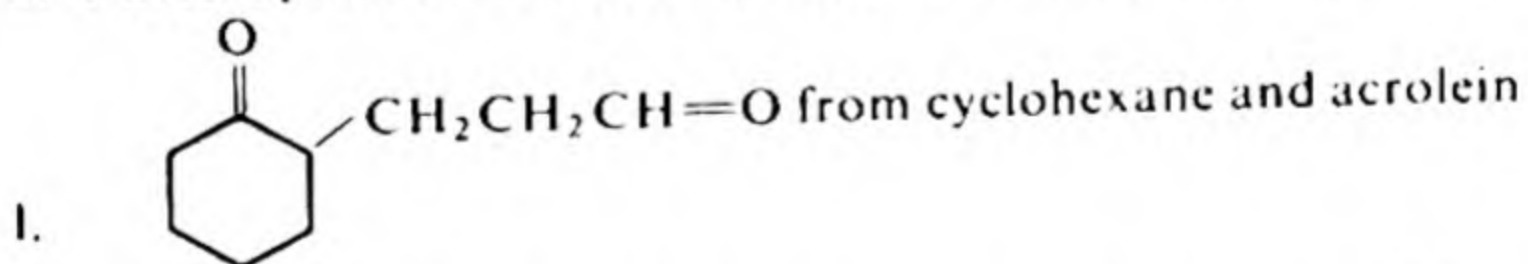
QUESTIONS AND PROBLEMS

1. Write equations for the reactions that occur when the following mixtures are treated under appropriate conditions. Specify conditions. Use structural formulas to represent organic compounds.

- | | |
|--|--|
| a. hydrazine hydrate and crotonaldehyde | g. <i>p</i> -nitrochlorobenzene and sodium sulfide |
| b. acetylene and <i>n</i> -propyl alcohol | h. <i>p</i> -dichlorobenzene and sodium hydroxide |
| c. phenylacetylene and phenol | i. 2,4-dinitrochlorobenzene and hydrazine |
| d. vinyl ethyl ether and ethanol | j. picryl chloride and ammonia |
| e. cyclohexanone and methyl methacrylate | |
| f. crotonaldehyde and <i>n</i> -butyl alcohol, 1 mole, in base | |

2. Show how the following compounds can be prepared in respectable yield from the suggested starting materials. Indicate necessary reagents, catalysts and conditions.

- ethyl acrylate from acetylene
- 1-chloro-1-ethoxyethane from acetylene
- 2,4-dinitroaniline from benzene
- anisole from chlorobenzene
- p*-cresol from toluene
- aniline from benzene by a process used only industrially. Name the process.
- 2,4-dinitrophenyl cyanide from chlorobenzene
- N*-2,4-dinitrophenylalanine from benzene and acetaldehyde. Alanine is α -aminopropionic acid.
- 2,4-dichlorophenoxyacetic acid from benzene and acetic acid
- ethylenediaminetetraacetic acid from acetylene
- δ -ketocaproic acid from acrylonitrile and ethyl acetate



- 3,5-dinitro-2-hydroxybenzaldehyde from 2,4-dinitrochlorobenzene and chloroform

23

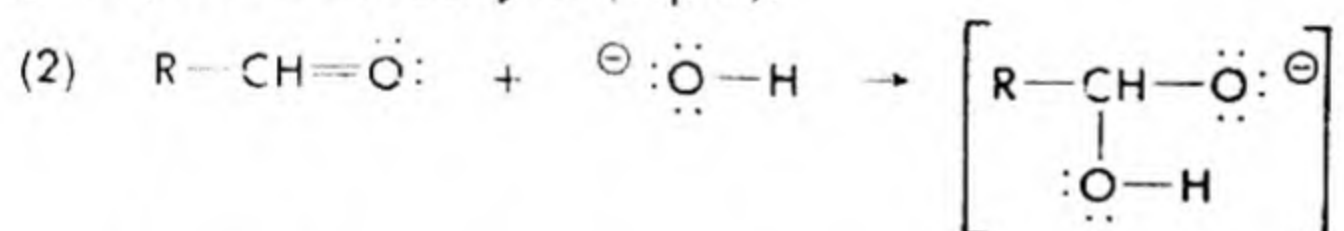
Oxidation-Reduction Systems which Involve Hydride Exchange

23-1 THE CANNIZZARO REACTION

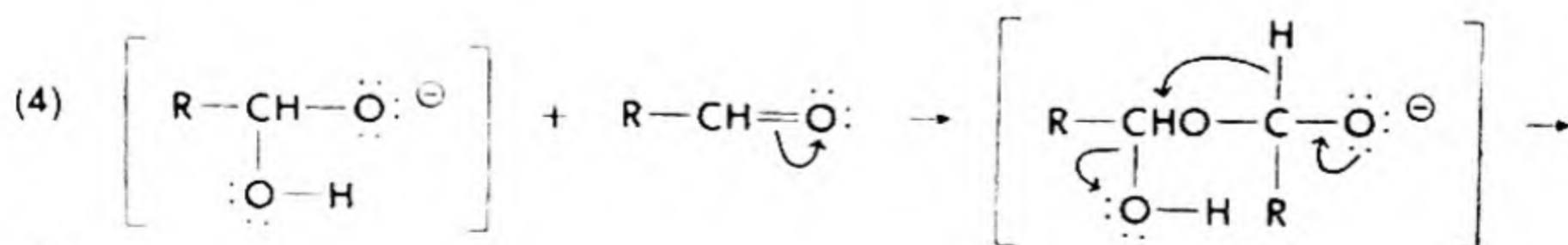
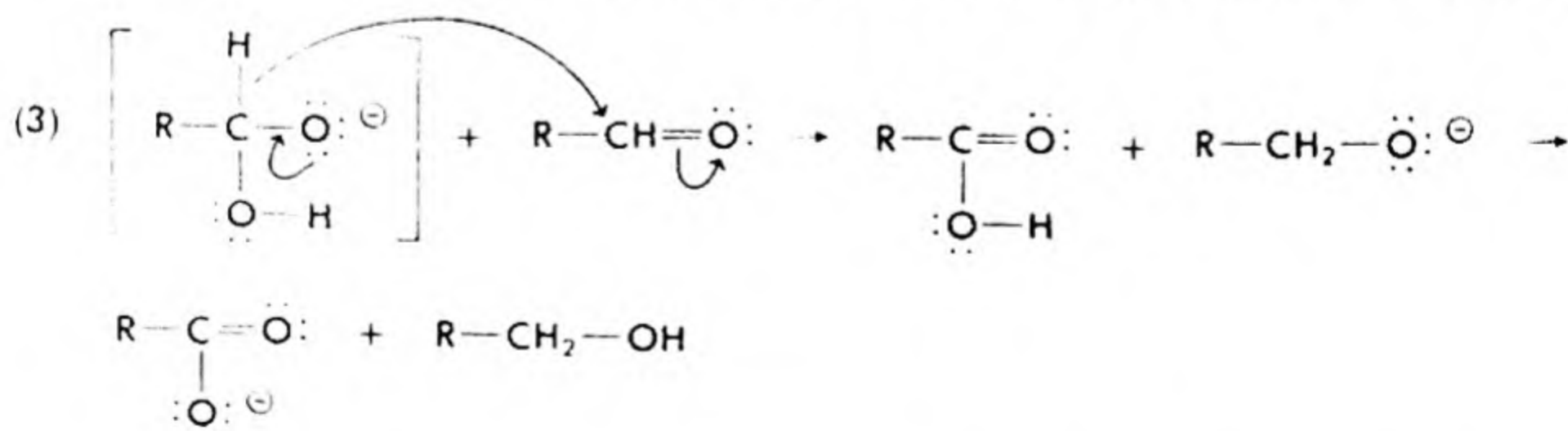
In alkaline solution aldehydes which have no alpha hydrogen atom, hence are incapable of aldol condensation, undergo a type of disproportionation called the *Cannizzaro reaction*. Shaking the pure aldehyde with sodium hydroxide solution causes 2 moles of the aldehyde to form a mole of the related alcohol and a mole of the related acid salt.

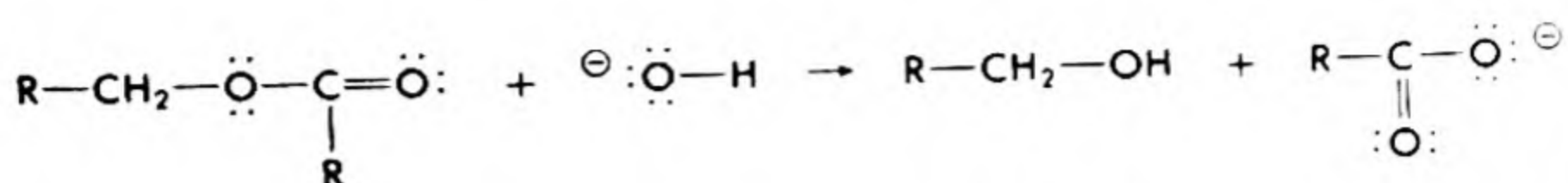


The reaction is initiated by addition of a hydroxide ion to the carbonyl group of the aldehyde (eq. 2).



This is followed by the transfer of a hydride ion, H^- , either to a separate molecule of aldehyde (eq. 3) or, after addition of the aldehyde-hydroxide complex to the second molecule of aldehyde, internally (eq. 4).

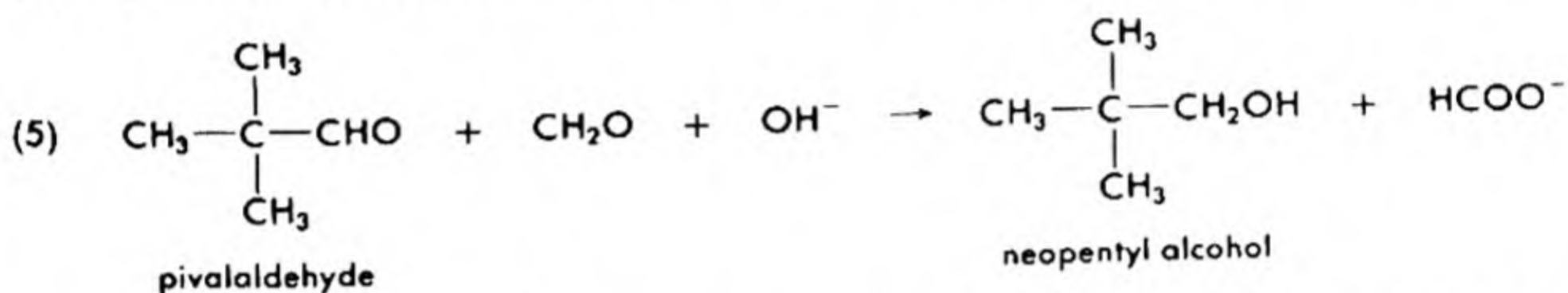




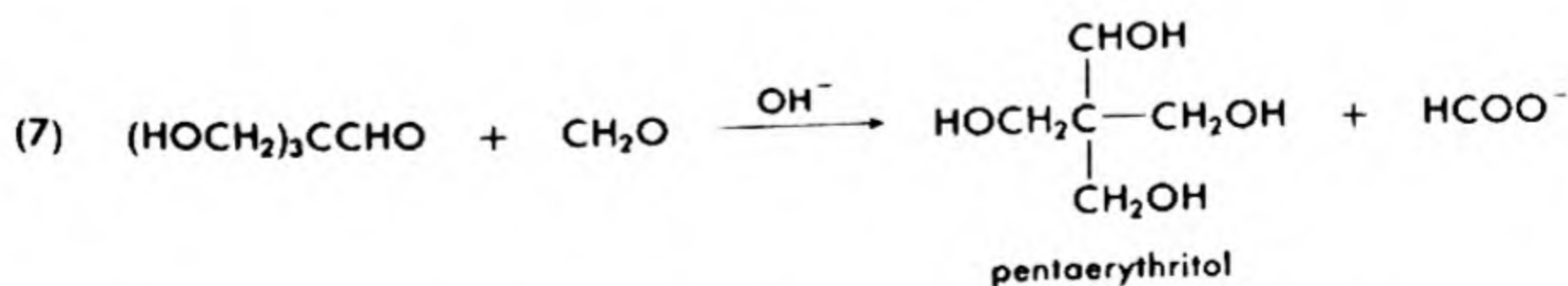
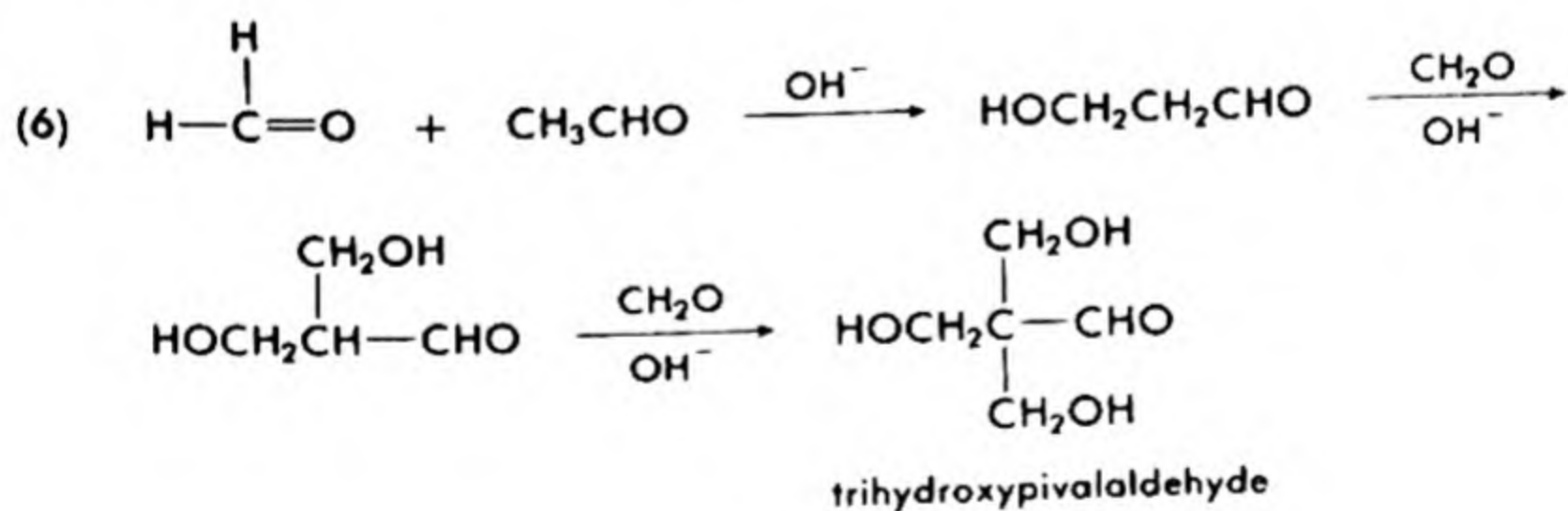
The reaction of formaldehyde gives methanol and formate; benzaldehyde gives benzyl alcohol and benzoate, etc.

A. The Crossed-Cannizzaro Reaction

When a mixture of formaldehyde and another aldehyde without α hydrogen atoms is treated under Cannizzaro conditions, the formaldehyde is oxidized to formate and the other aldehyde is reduced to the corresponding alcohol. Thus, pivalaldehyde is reduced to neopentyl alcohol (eq. 5). This is termed the *crossed-Cannizzaro reaction*. An interesting



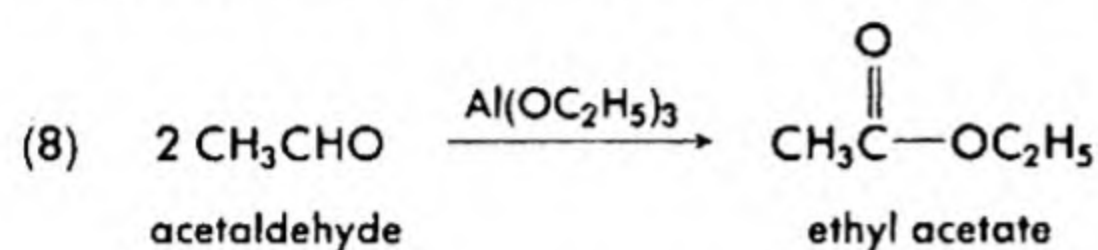
industrial application of this reaction as well as of the aldol condensation (see §21-4D) is seen in the preparation of pentaerythritol. Acetaldehyde undergoes three aldol condensations with formaldehyde until all of the active hydrogens are utilized (outline 6). The trihydroxypivalaldehyde which results then undergoes a crossed-Cannizzaro reaction with more formaldehyde (eq. 7).



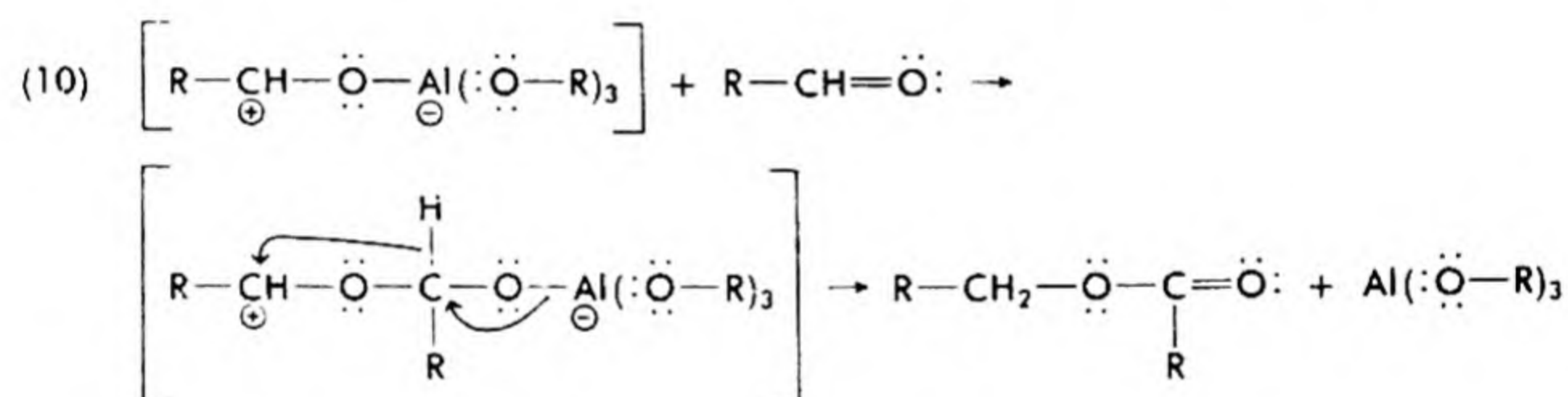
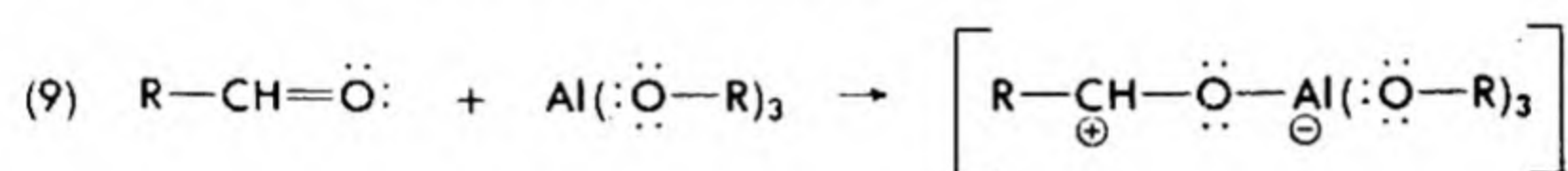
This tetrahydric alcohol is used in the preparation of plastics and to make pentaerythritol tetranitrate, PETN, a high explosive.

23-2 THE TISHCHENKO REACTION

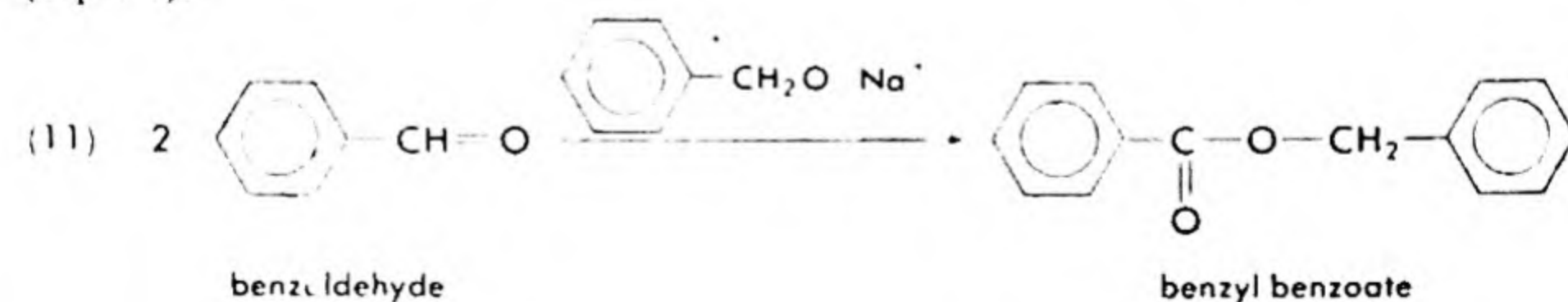
The Tishchenko reaction is formally similar to the Cannizzaro reaction in the oxidation-reduction sense. The Tishchenko reaction is carried out in the absence of water, using as catalyst a solution of aluminum alkoxide in alcohol. Under these conditions, even aldehydes with alpha hydrogen atoms undergo disproportionation. The product is a mole of ester of which the alkyl group originates from one molecule of the original aldehyde and the acyl group from another. An example is given in eq. (8),



The mechanism of the reaction involves the function of aluminum alkoxide as a Lewis acid. Reaction conditions prevent hydrolysis of the ester as in the Cannizzaro reaction.



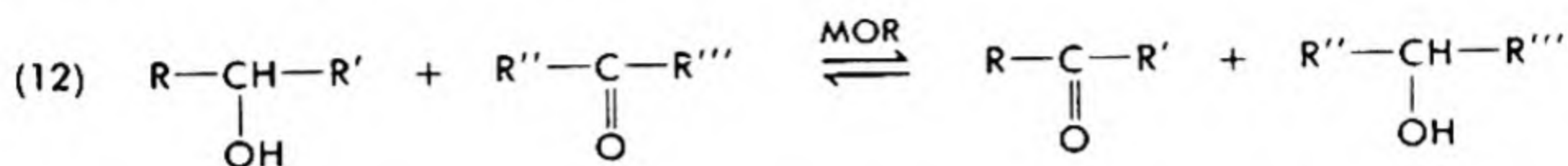
The use of more basic alkoxides causes attack on the alpha hydrogen in aldehydes that have one, leading to condensations and mixed condensation-dismutation reactions. However, even a sodium alkoxide is used successfully to give a 93% yield of benzyl benzoate from benzaldehyde (eq. 11).



23-3 THE MEERWEIN-PONNDORF-VERLEY AND OPPENAUER REACTIONS

The fact that alcohols and aldehydes or ketones are related intermediate oxidation stages of carbon compounds suggests the possibility that, under

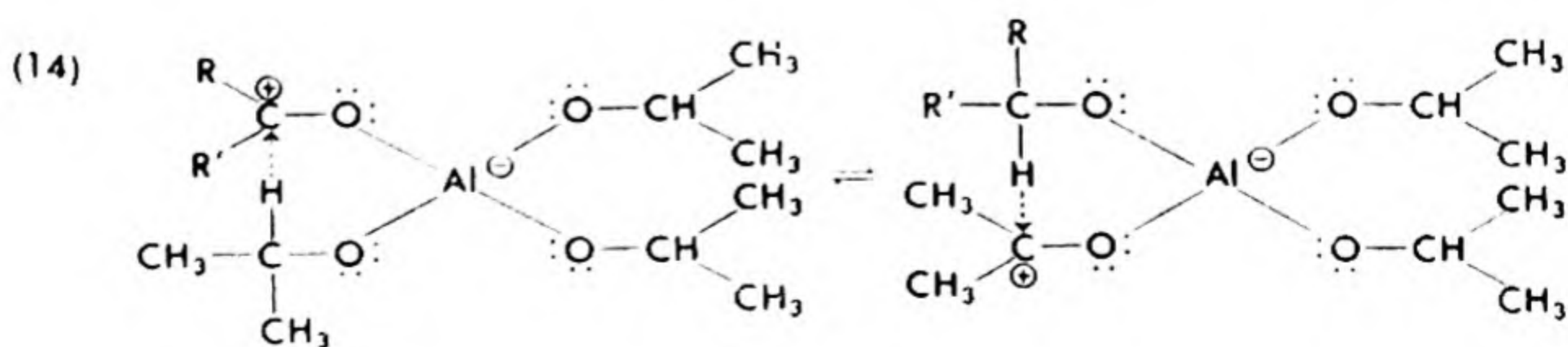
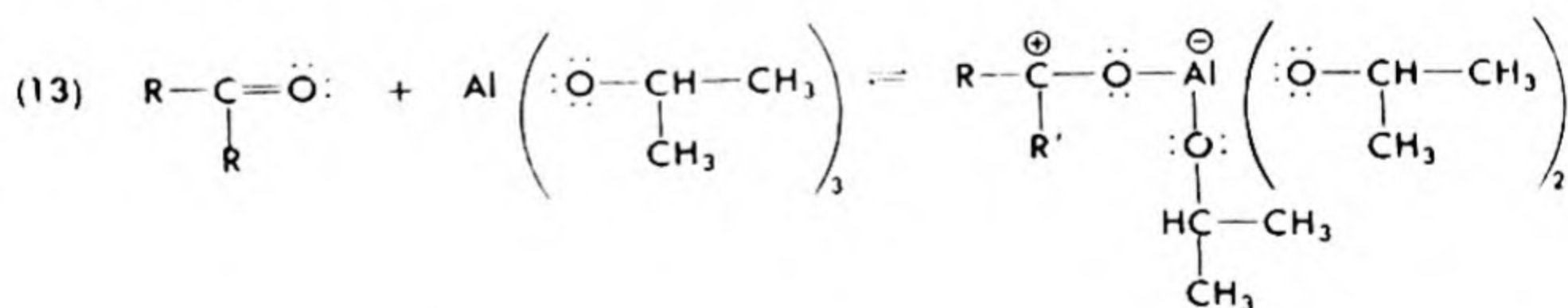
suitable conditions, an equilibrium might be established between an alcohol and the related aldehyde or ketone. Meerwein showed that metal alkoxides catalyze the formation of just such an equilibrium between two alcohols and their related carbonyl compounds (eq. 12). The most common catalyst for the reaction, when isopropyl alcohol is used as the reduc-

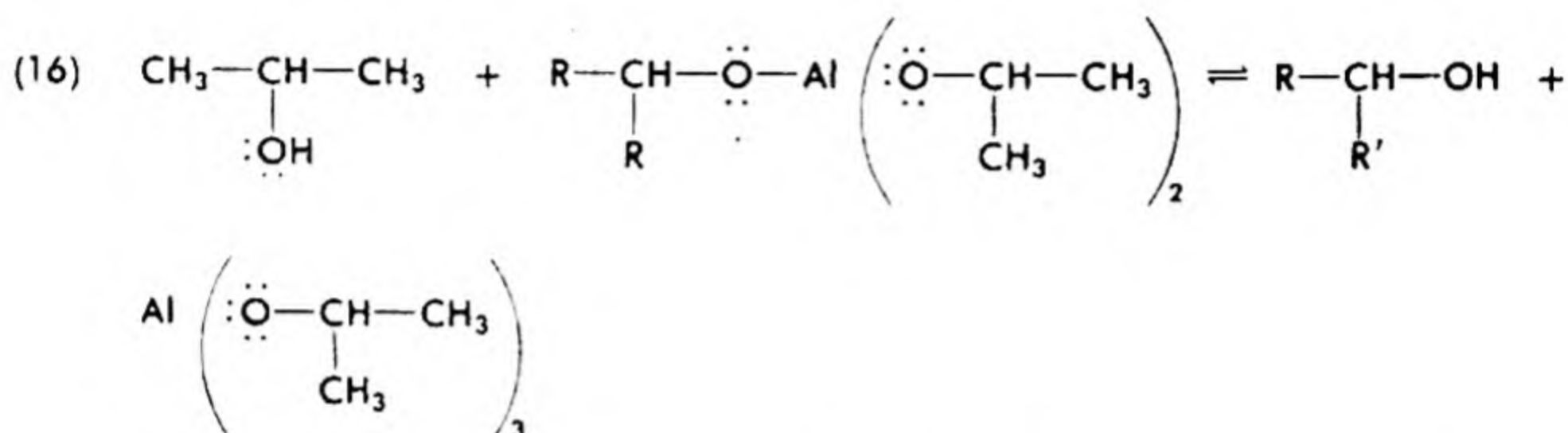
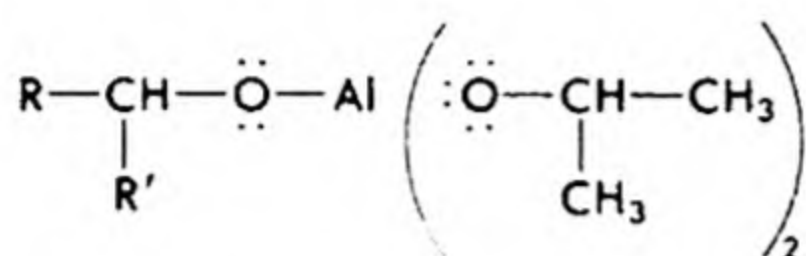
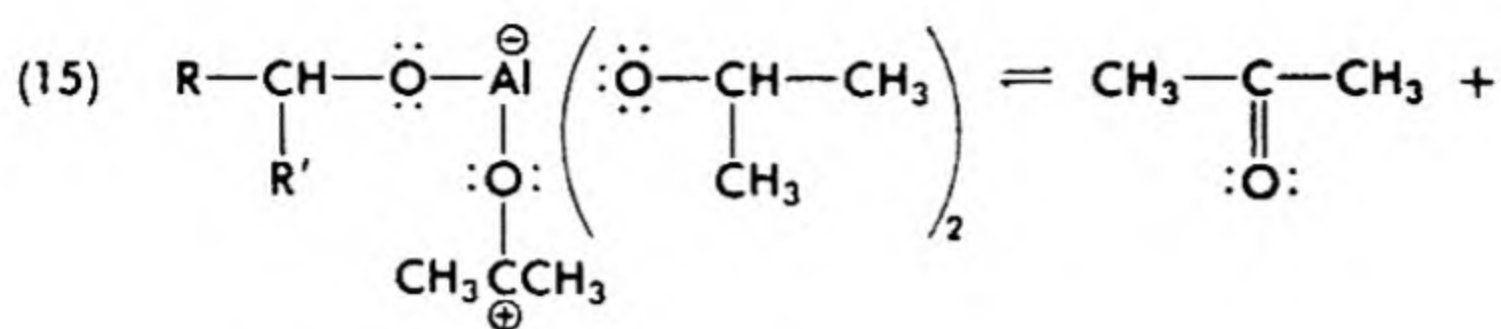


ing agent, is aluminum isopropoxide. The Meerwein-Ponndorf-Verley reaction is the use of isopropyl alcohol and aluminum isopropoxide to reduce an aldehyde or ketone. Its usefulness lies in the fact that only the carbonyl group is reduced. Most other reducible groups are not attacked. An exception is the very readily reducible nitro group. Since the equilibrium (eq. 12) is not complete in either direction, the success of the Meerwein-Ponndorf-Verley reaction depends on use of excess isopropyl alcohol and complete removal of the product acetone by selective distillation. The method fails for reduction of aldehydes that are lower-boiling than acetone.

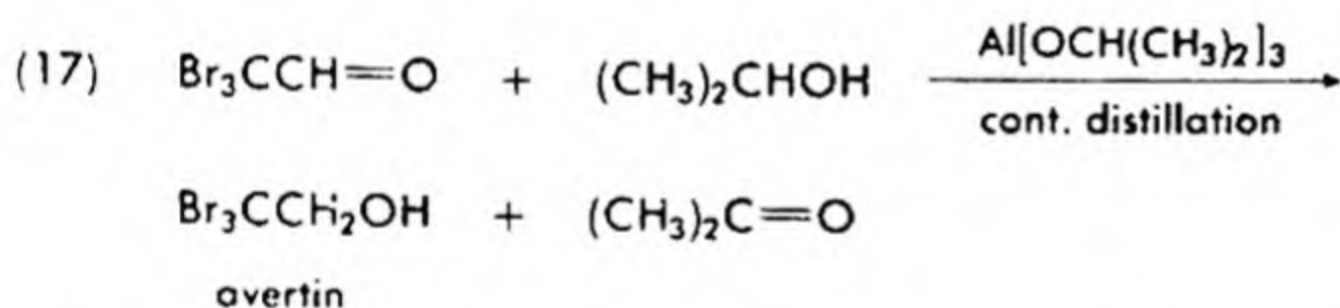
Oppenauer introduced the use of the reverse direction of the reaction. Hydroxy groups can be selectively oxidized in the presence of other even more readily oxidized groups by use of a very large excess of acetone and aluminum isopropoxide.

The mechanism of the reaction is quite similar to that of the Tishchenko reaction. The shift of a hydride ion from one to another of two groups on the aluminum atom establishes equilibrium between the oxidized and reduced forms (eq. 14).





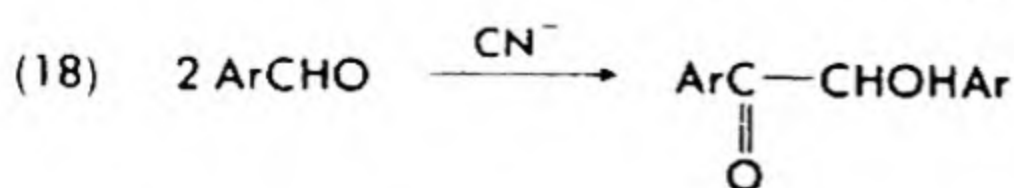
Side reactions in both the Meerwein-Ponndorf-Verley reduction and the Oppenauer oxidation are remarkably few. Even halogen atoms remain in most cases, for example, the reduction of bromal to the rectal anesthetic, avertin (2,2,2-tribromoethanol) (eq. 17).



Other ketones (e.g., cyclohexanone or benzoquinone) or alcohols may be used as oxidizing or reducing agents for special reasons.

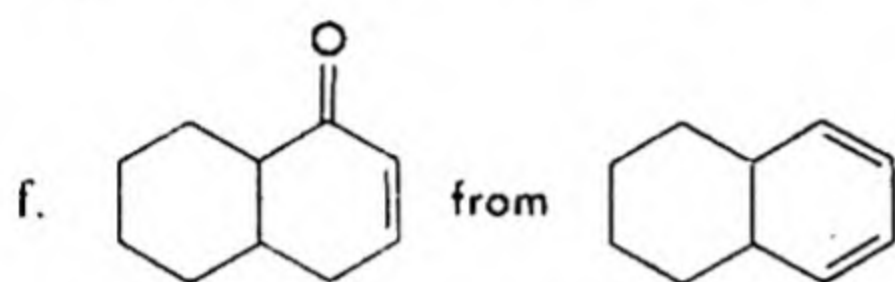
23-4 THE BENZOIN CONDENSATION

In an alcoholic solution of sodium cyanide or potassium cyanide, an aromatic aldehyde undergoes a type of condensation which involves oxidation-reduction. This condensation is similar to the preceding reactions in that it is a base-catalyzed oxidation-reduction; however, no hydride ion migration occurs. Cyanide ion is a specific catalyst; no other is effective. A possible mechanism is given.



2. Show how the following syntheses can be performed as advantageously as possible from the indicated starting materials and inorganic reagents. Use structural formulas for organic compounds. Indicate all necessary reagents, catalysts, and special conditions.

- a. ethyl acetate from acetylene
- b. 2-hydroxymethyl-2-methyl-1,3-propanediol from *n*-propionaldehyde and methanol
- c. di- β -styrylcarbinol from benzaldehyde and acetone
- d. *p*-propionylbenzaldehyde from *p*-(dichloromethyl)benzaldehyde and ethanol
- e. *p,p'*-dinitrobenzoin from toluene



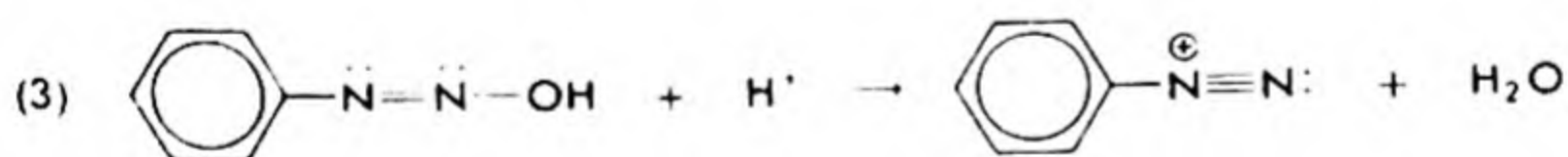
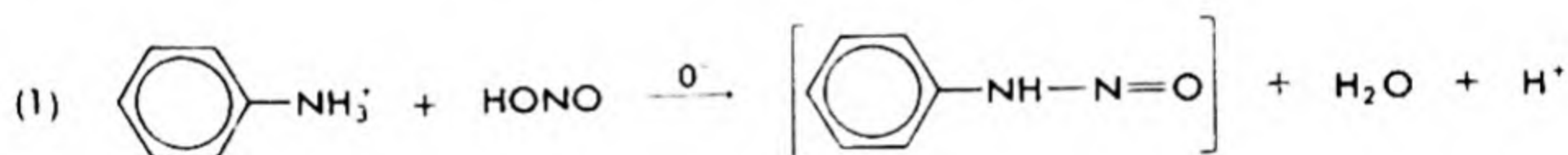
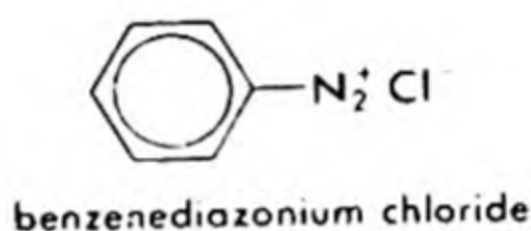
- g. benzyl benzoate from toluene
- h. phenyl cyclopentyl ketone from benzaldehyde and bromocyclopentane
- i. 1,3-butanediol from acetaldehyde and isopropyl alcohol
- j. 2,2-dimethyl-1,3-propanediol from isobutyraldehyde and formaldehyde

24

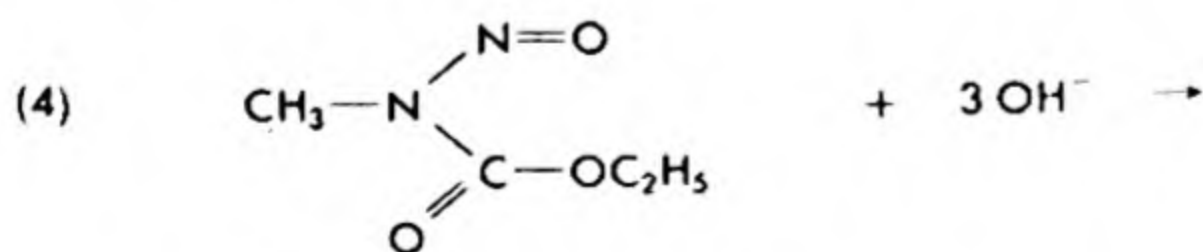
Diazonium Compounds and Diazo Compounds

24-1 PREPARATION

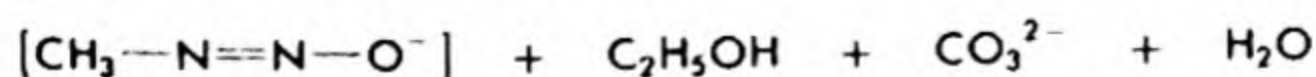
Arenediazonium salts, of which benzenediazonium chloride is typical, are prepared by *diazotization* of an aromatic primary amine. This is the treatment of the amine with a source of nitrous acid at a temperature low enough to prevent decomposition of the diazonium salt, usually in the neighborhood of 0°.

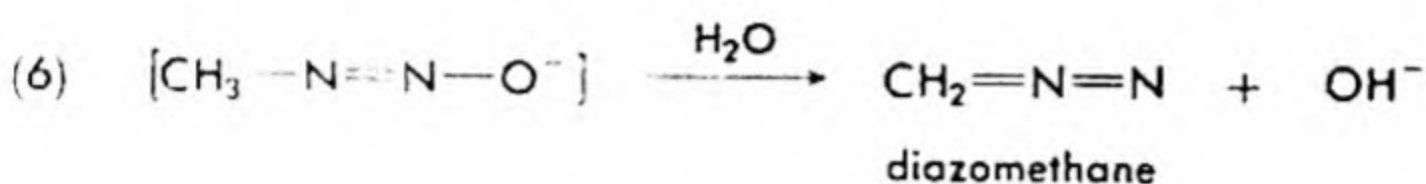
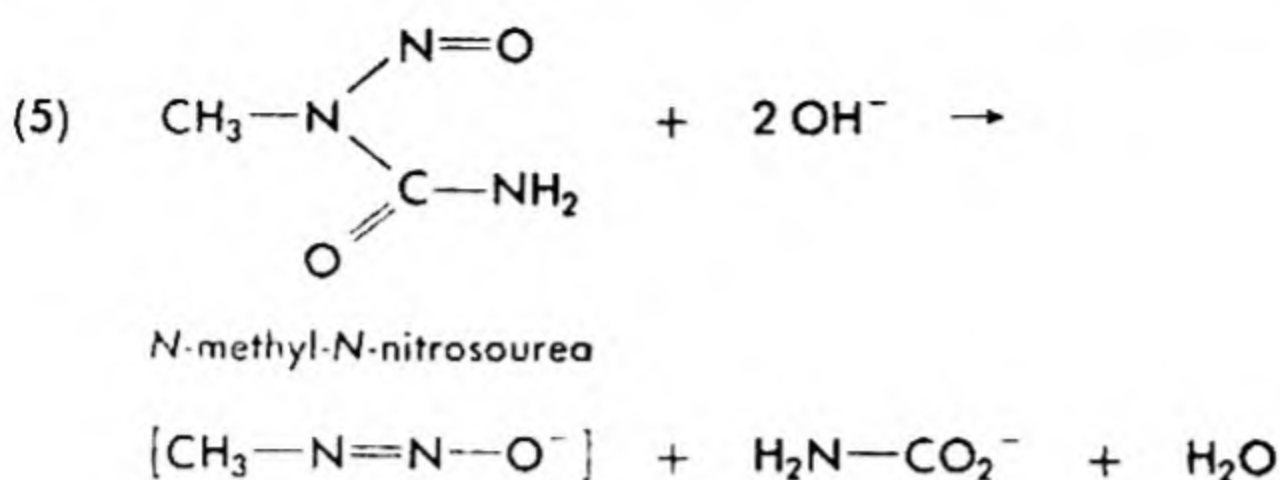


Diazo compounds, of which diazomethane is the most commonly used, are prepared from acyl nitrosoamines such as nitrosoalkylurethanes or nitrosoalkylureas (eqs. 4-6).

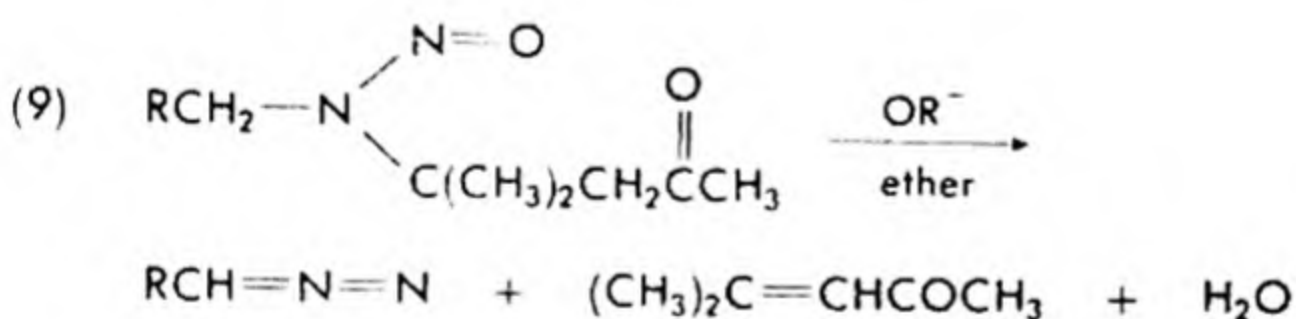
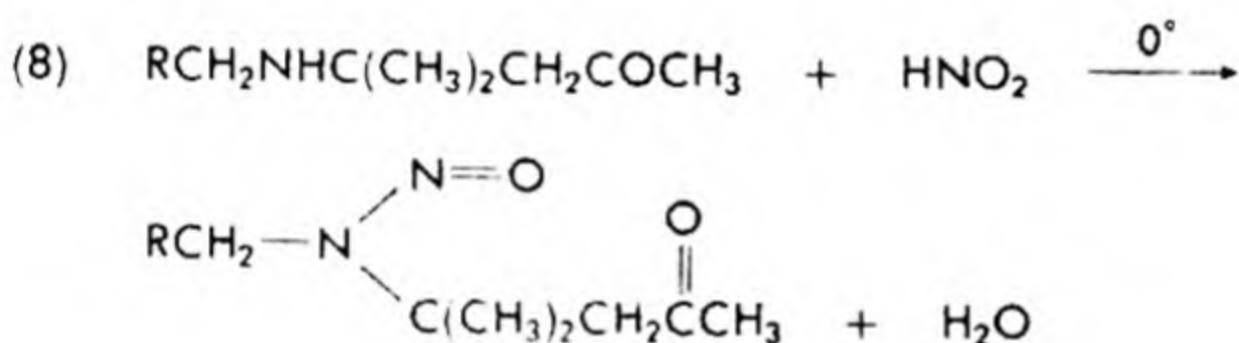
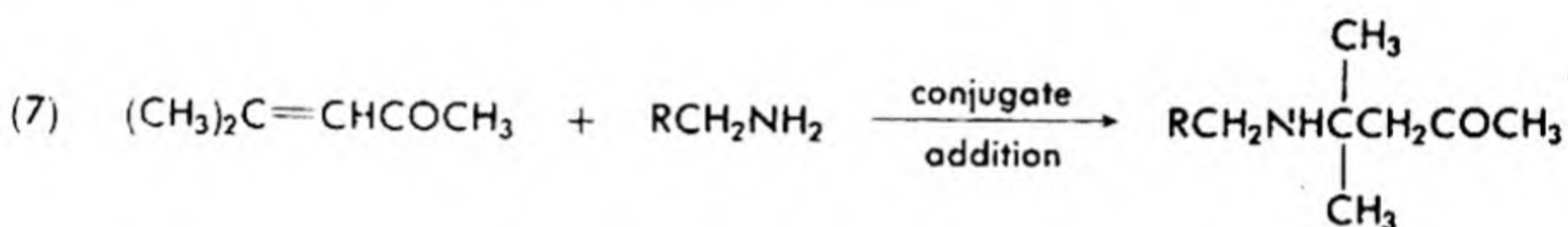


ethyl N-methyl-N-nitrosocarbamate





A general method useful for the preparation of higher diazoalkanes utilizes mesityl oxide and a primary amine (eqs. 7-9).

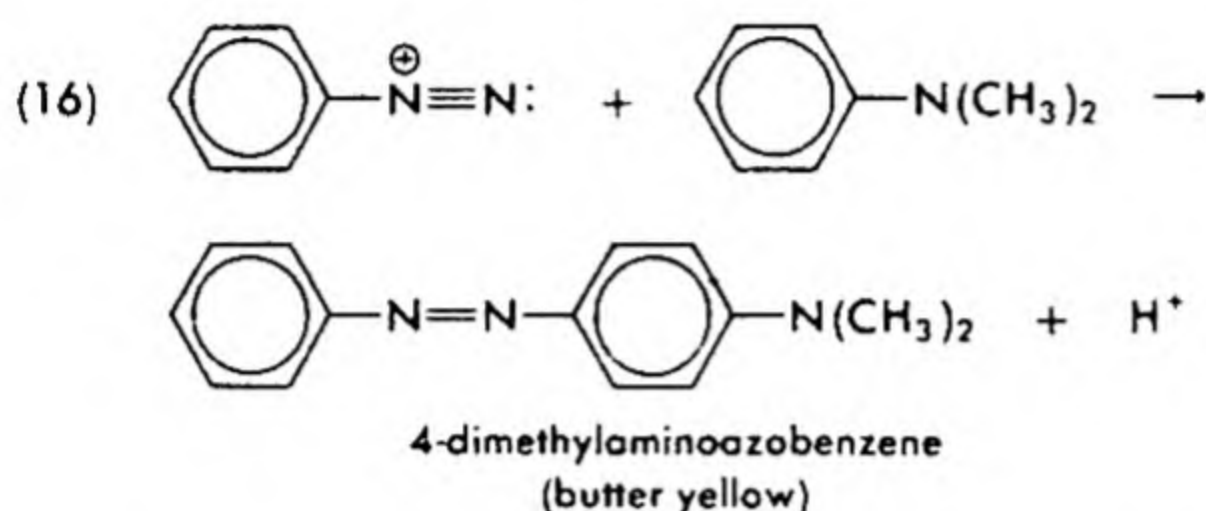
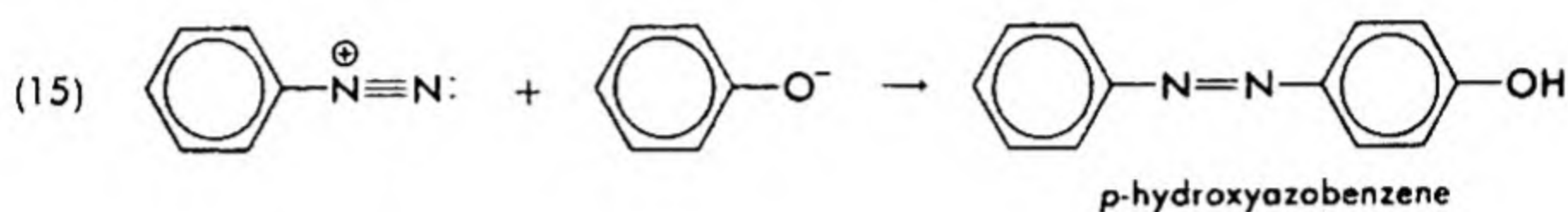


24-2 PROPERTIES AND REACTIONS OF DIAZONIUM SALTS

Arenediazonium salts are stable for short times in solution at low temperatures. Salts of fluoboric acid are stable enough to be isolated and stored in the dark at ordinary room temperatures.

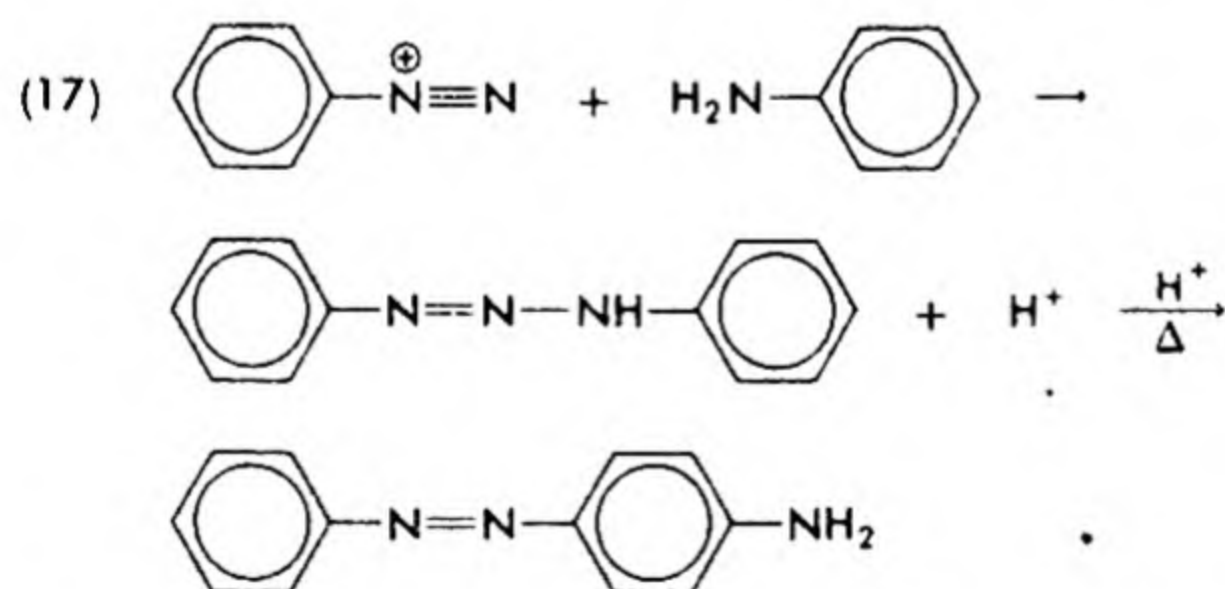
The relative stability of arenediazonium salts is notable. Alkanediazonium ions are too unstable to be kept or isolated even at -80° ; upon formation, they decompose to carbonium ions, which undergo all of the typical carbonium ion reactions (nucleophilic attack, elimination of hydrogen ions, rearrangements). Even bridgehead carbonium ions, such as I, are quickly produced by this route (eq. 10), though such ions, strained out of trigonal planar geometry, are very difficult to obtain in other reactions which normally proceed via carbonium ions.

preferably in the *para* position. Only when the *para* position is occupied does the diazonium group attack the position *ortho* to the amino or hydroxy group. The substitution of a diazo group in an aromatic amine or phenol is called *coupling*.



Careful control of pH is required for best yields of coupling products. The species ArN_2^+ must be available, which requires a pH that is not too high. However, the species ArO^- or ArNR_2 must also be present, which requires a pH that is not too low. A buffer can be used to provide the optimum pH.

Primary arylamines give diazoamino compounds. These can be re-arranged to the azo compounds by heating in acid solution.



Azo compounds are highly colored. Those with groups on the benzene ring suitable for associating with groups in textile fiber molecules are dyestuffs.

Certain diazonium salts which are stable to moderate heating when kept dry and out of the light have been developed. Paper coated with a mixture of stable diazonium salt and coupling agent can be used for photocopying. When exposed to ultraviolet light, the diazonium salt on the paper is destroyed except where protected by the lines of a drawing or black letter-

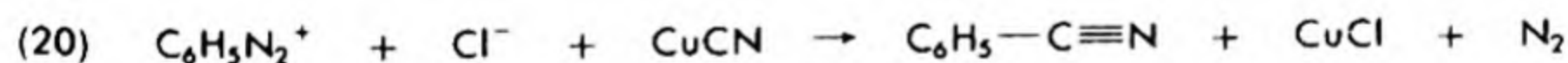
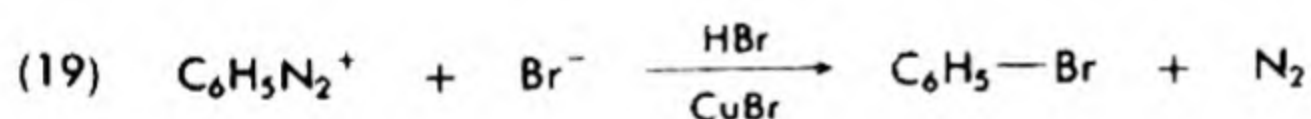
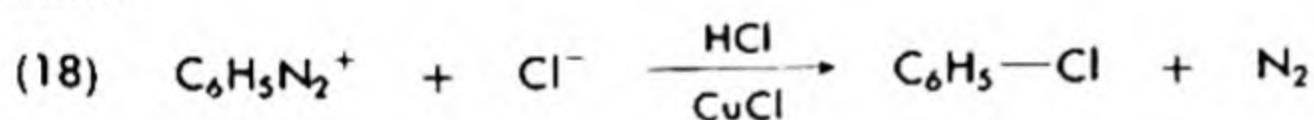
ing. The dye is developed by passing the paper through moist ammonia fumes; a positive print results. This is called the Ozalid process.

B. Sandmeyer and Related Reactions

Because of the low reactivity of typical aryl halides, reactions other than halogen replacement have been necessary for the preparation of many aromatic compounds. Since arenediazonium salts are very reactive, these can serve many of the same functions that halides serve in the aliphatic series. The *Sandmeyer reactions* and modifications thereof are means by which these replacements can be executed.

The mechanisms of Sandmeyer reactions are still open to question. While carbonium ions may be involved, at least in some of these displacements, there is also evidence which may require other explanations. Hence, no speculation on this point is presented here. Typical Sandmeyer replacements are represented in eqs. (18) through (20). The group that substitutes into the ring is that which was associated with the acid and cuprous ion, not that of the diazonium salt. Nevertheless, it may be advantageous to prepare the diazonium salt of the halide to be replaced, as the other anion may interfere. Alternatively, the diazonium sulfate may be used, since sulfate ions do not participate in the replacement.

The Sandmeyer reactions are particularly useful for the preparation of substituted aromatic compounds not readily prepared by direct substitution.

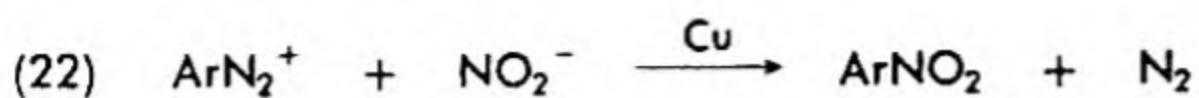


Yields of various chloro and cyano derivatives of toluene from the corresponding toluidines are in the neighborhood of 70–80%. Similar yields of *m*-chloro- and *m*-bromobenzaldehydes are obtained by the Sandmeyer reaction from *m*-aminobenzaldehyde.

(1) *Gattermann's Modification.* Ludwig Gattermann discovered that it is unnecessary to prepare the cuprous salt. Copper powder can be used to catalyze replacement of the diazonium group directly from an acid. This modification is of interest industrially since it makes unnecessary the consumption of expensive cuprous salts.

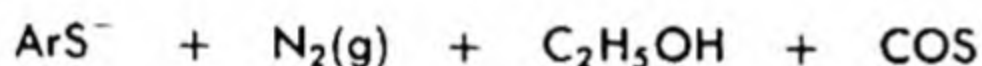
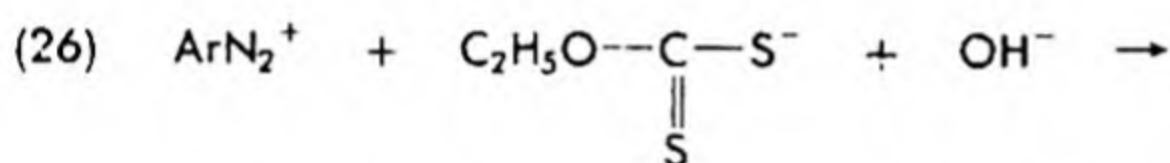
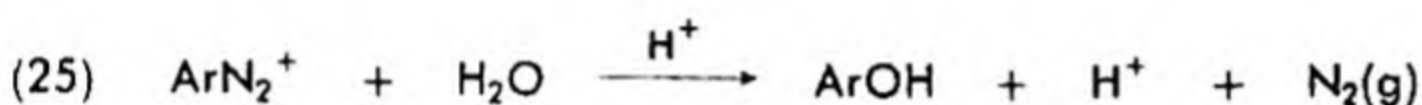
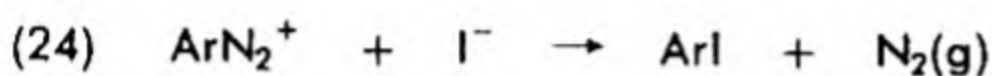


The *Gattermann modification* can be extended to the preparation of other derivatives of aromatic compounds. The preparation of nitro com-



pounds impossible to make by substitution is effected by sodium nitrite treatment (eq. 22). *p*-Dinitrobenzene can be prepared in 67–82% yield, and *o*-dinitrobenzene in 38% yield.

(2) *Other Replacements.* Diazonium salts react with fluoboric acid, hydriodic acid, and slightly acidic aqueous solutions to replace the diazonium group by fluorine, iodine, or a hydroxy group, respectively (eqs. 23–25).

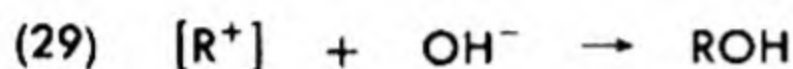
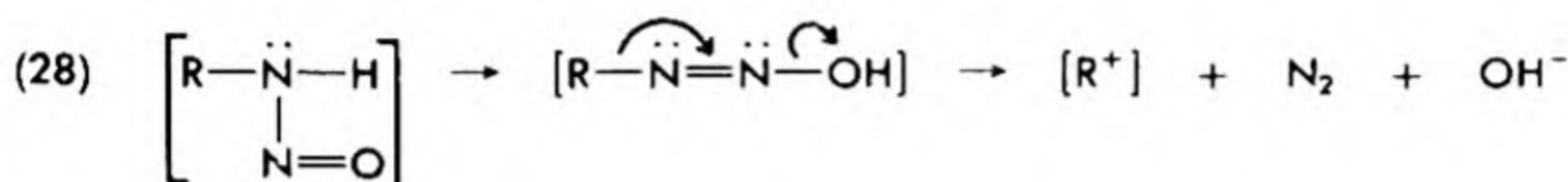
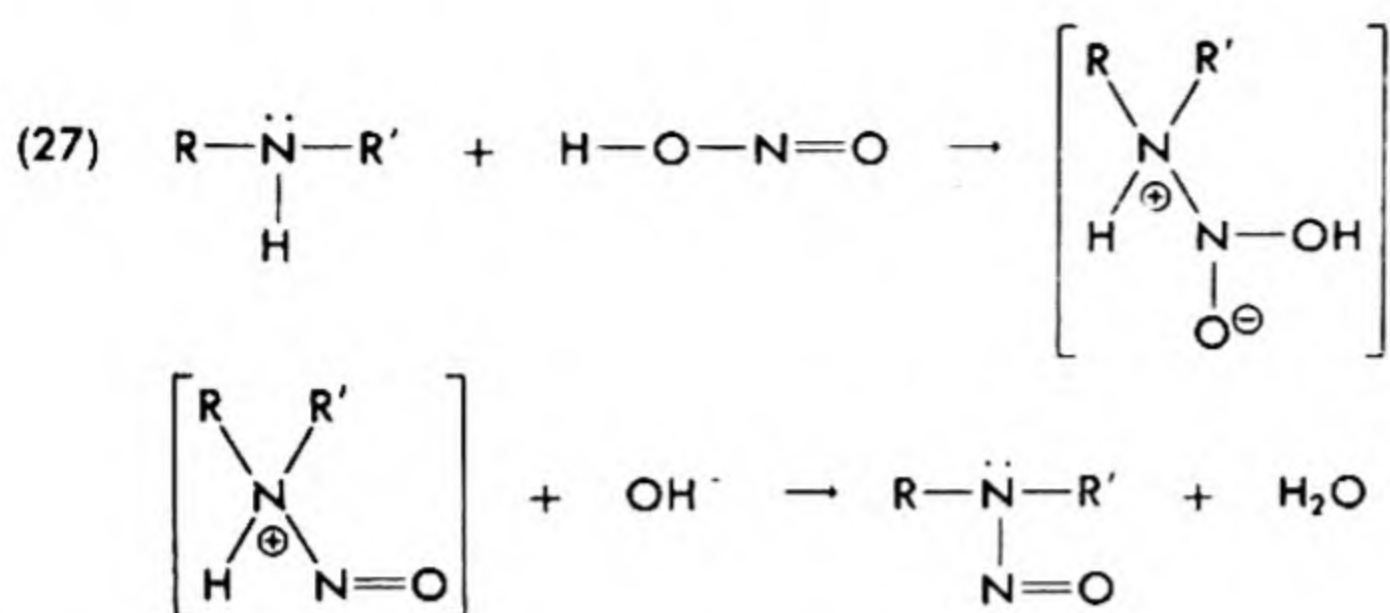


Sodium or potassium xanthate replaces the diazonium group with the mercapto group (eq. 26). Sodium sulfide has been used occasionally in place of the xanthates, but this practice is dangerous, since insoluble diazonium sulfides often precipitate and explode.

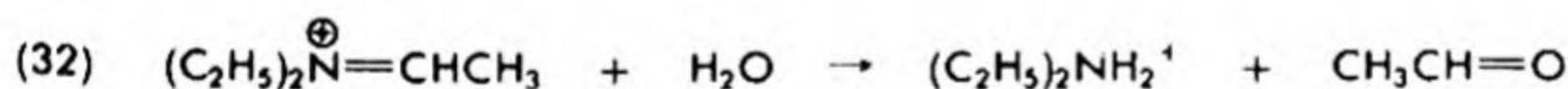
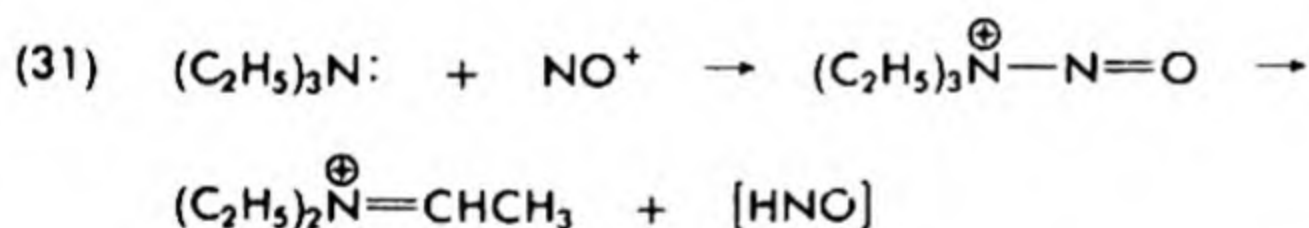
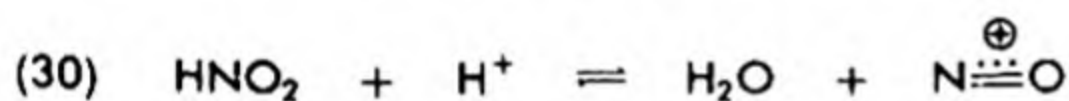
(3) *Reactions of Nitrous Acid with Aliphatic Amines and Amides.* As was stated before (§24-2), alkanediazonium compounds are intermediates of very short lifetimes, which decompose to carbonium ions. Since diazotization of a primary amine is commonly carried out in water in the presence of hydrochloric acid and nitrite ions, it can be anticipated that alcohols, both normal and rearranged, and olefins will be the main products of the reaction, with smaller amounts of normal and rearranged alkyl chlorides, nitrites, and nitro compounds.

The reaction of nitrous acid with amides is much less complex, since it generally leads to a good yield of the carboxylic acid. In either case, however, the use of this reaction as an analytical tool depends on the quantitative evolution of nitrogen, not on the quantitative production of organic products.

Light is shed on the mechanisms of reactions of primary amines with nitrous acid by the reactions of secondary amines. These compounds (both aliphatic and aromatic) give nitrosoamines. Hence, nitrosoamines are considered to be the precursors of diazo hydroxides (§24-2). When R' (eq. 27) is H, further rearrangement occurs (eq. 28).

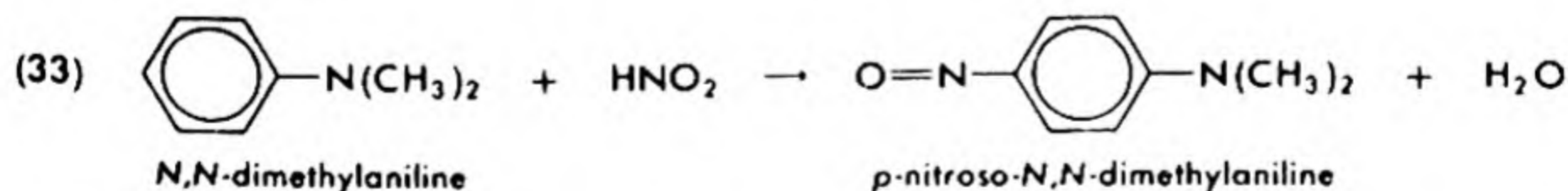


Tertiary aliphatic amines have often been said to be inert to nitrous acid. This is true only for cold solutions of low pH (less than 3), in which virtually all of the amine has been converted to its ammonium salt. At higher pH (3-6), the amine is attacked with cleavage of one alkyl group from the nitrogen atom to form a secondary alkyl nitrosoamine and products of the cleaved alkyl group. The secondary amine produced in eq. (32)



behaves then as expected from eq. (27). The nitroxyl (HNO) produced in eq. (31) forms nitrous oxide. The reaction course is believed to be that of eqs. (30) to (32).

Tertiary aromatic amines undergo electrophilic substitution under similar conditions.

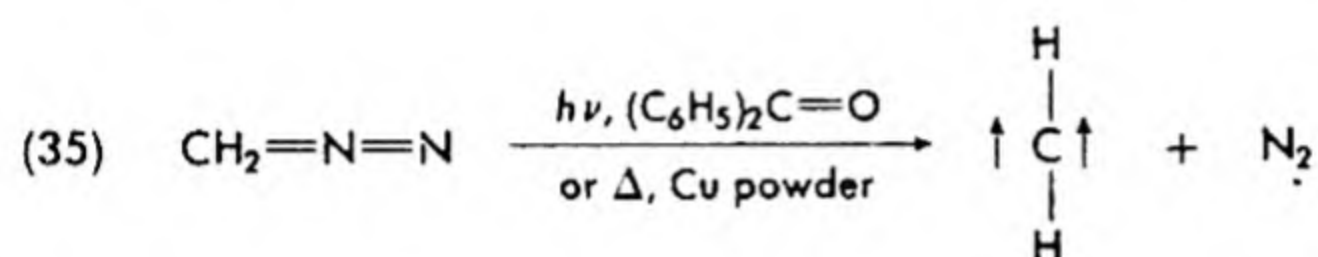
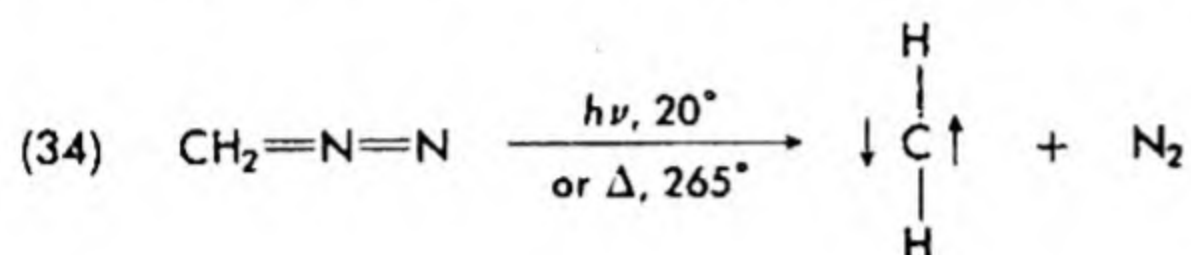


24-3 PROPERTIES AND REACTIONS OF DIAZO COMPOUNDS

Diazo compounds have a well-earned reputation for instability. They are normally handled in dilute ether solutions and are purified by distilla-

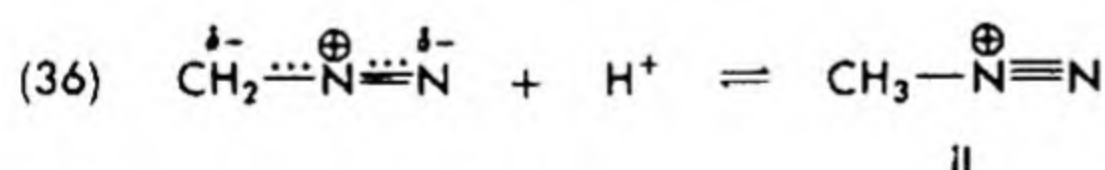
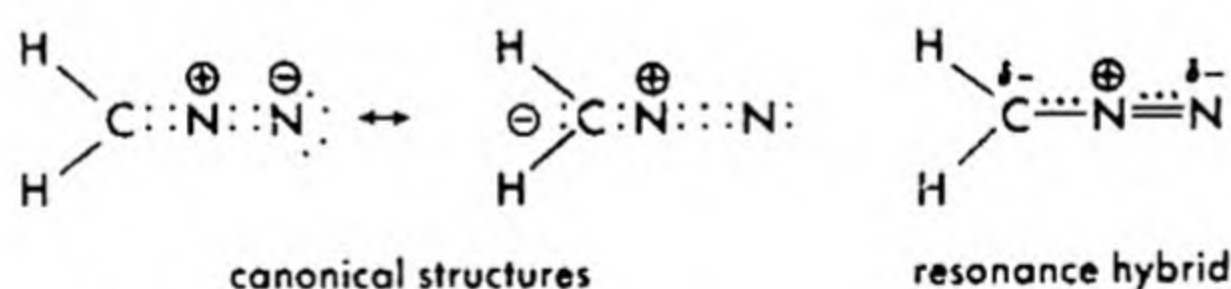
tion in such a way that the vapors contain a little diazo compound in ether. Whenever diazo compounds are allowed to concentrate in the still-pot, in the vapors or in the condensate, a detonation is probable.

As noted before (§13-5A), photolysis or pyrolysis of diazomethane gives methylene. Uncatalyzed photolysis or pyrolysis gives a highly reactive species with the unshared electrons having antiparallel spins (eq. 34). Photolysis with a photosensitizer or catalytic pyrolysis (eq. 35)



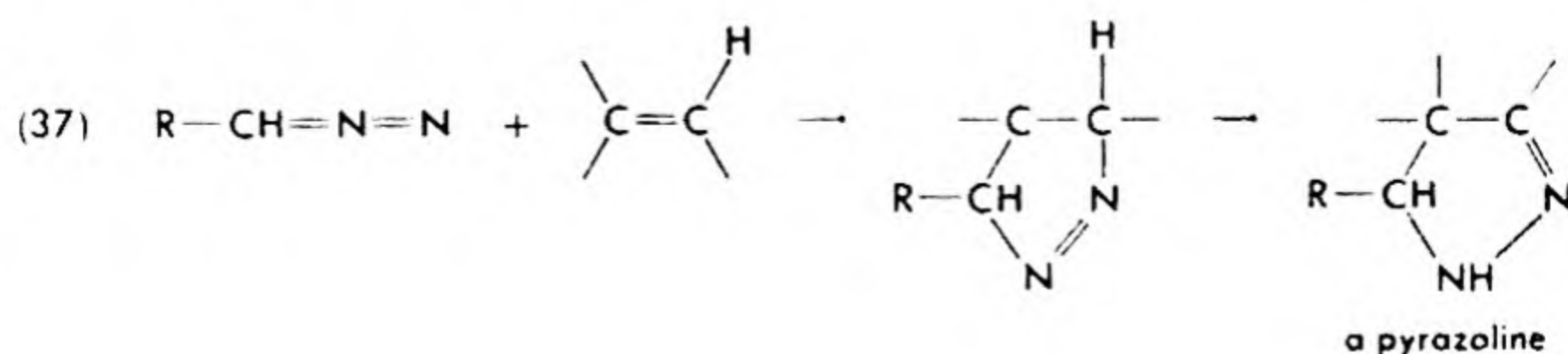
gives a somewhat less reactive diradical with the unshared electron spins parallel. Thus, the photochemical or pyrolytic reactions of diazomethane depend to some extent on the manner of decomposition.

Not all reactions of diazoalkanes involve their decomposition to carbenes. Diazomethane and other diazoalkanes are active nucleophilic reagents due to resonance structures which place negative character on the carbon atom. In addition, diazomethane easily accepts a proton to form the electrophilic species, II.

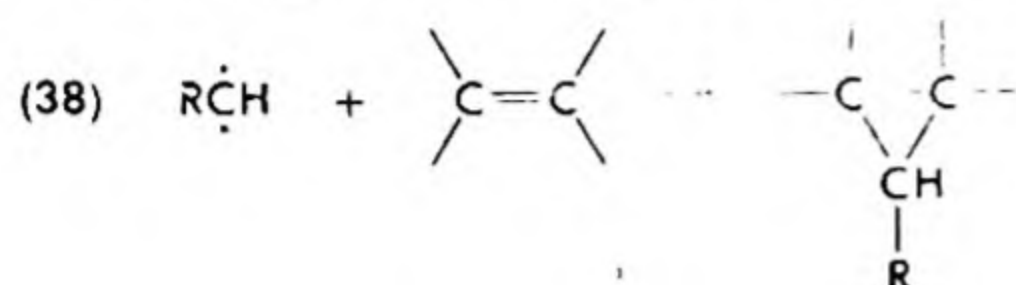


A. Addition to Olefins

A cold solution of diazoalkane reacts with an olefin to form a 1,2-diazoline (pyrazoline).

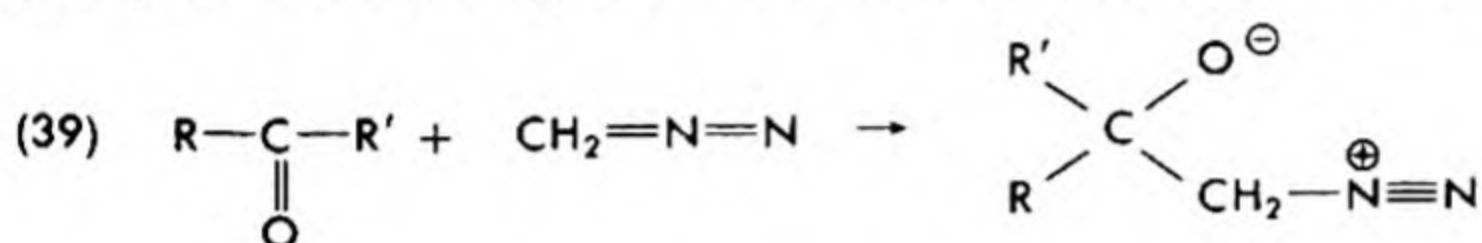


Irradiation with a sensitizer or catalytic decomposition of a diazoalkane gives a carbene which adds to form a cyclopropane derivative (eqs. 35 and 38). Configurations of groups from the olefin are mixed in the product.

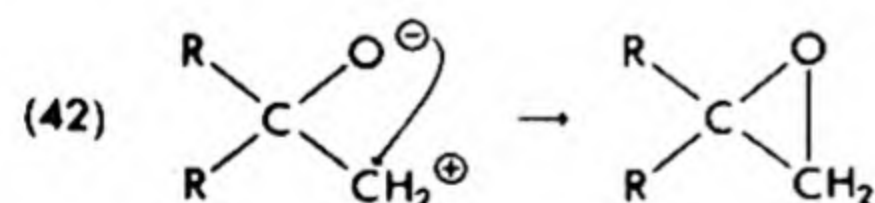
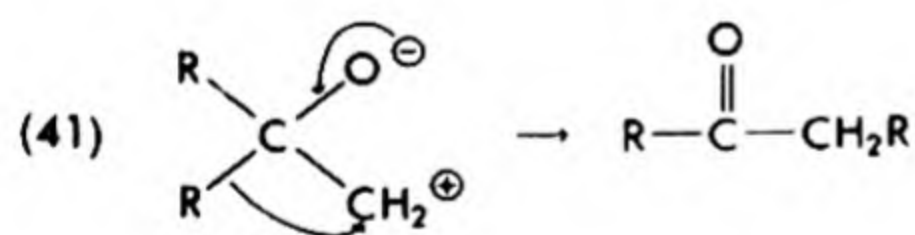
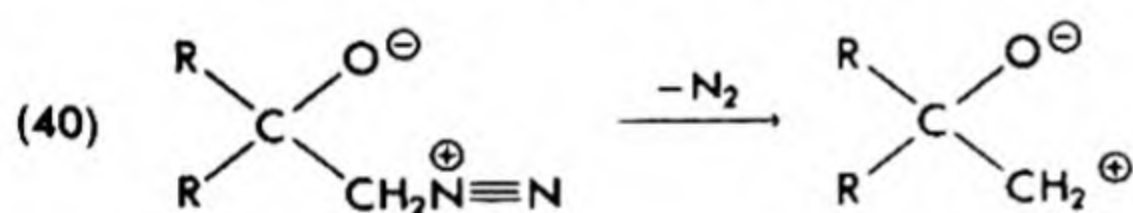


B. Insertion Reactions

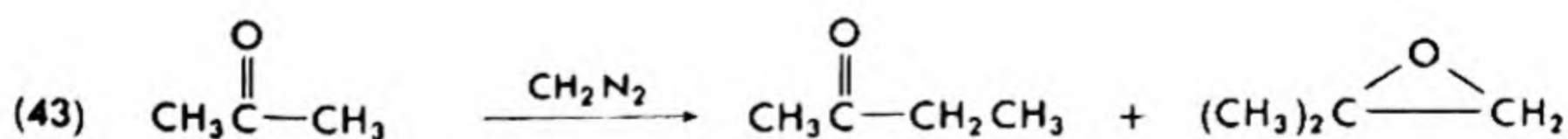
Diazomethane is useful for extending chain lengths of carbonyl compounds by insertion of methylene units. It is assumed that the carbonyl group suffers nucleophilic attack by diazomethane. The resulting dipolar



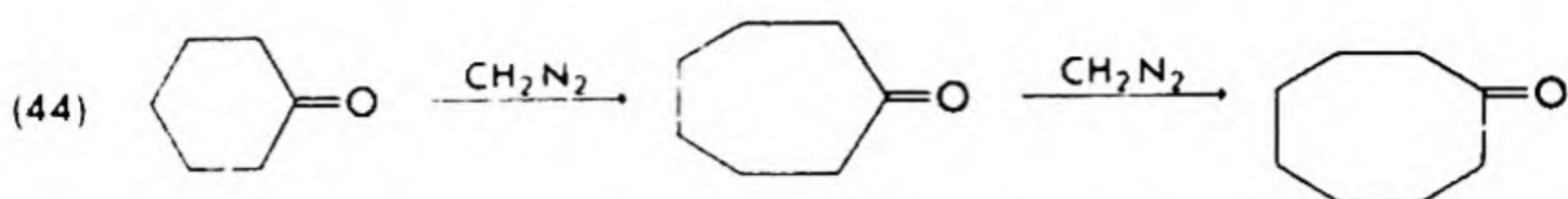
compound eliminates nitrogen to give an intermediate which may rearrange or may close to an epoxide. The sequence suggested in eqs. 39 to 42 remains to be established (e.g., certain of the steps may be concerted). Similar reactions occur with aldehydes.



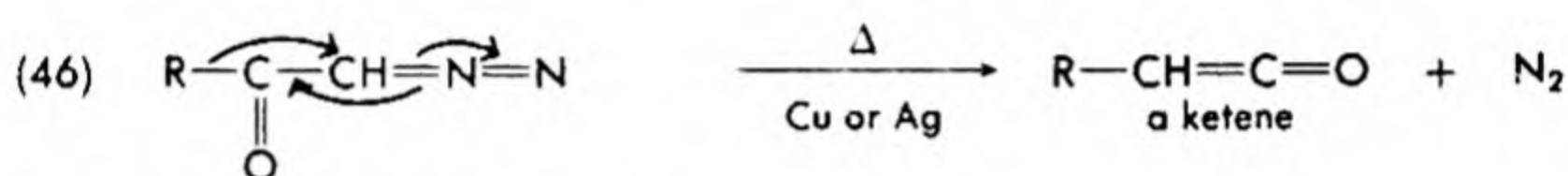
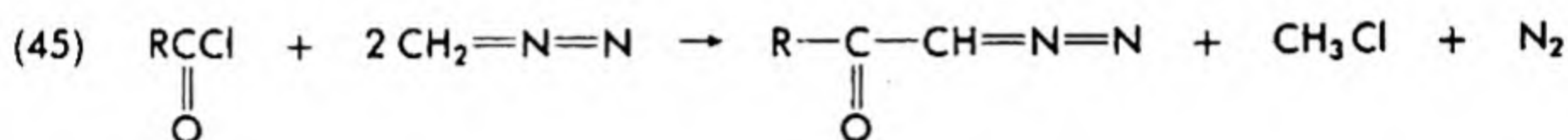
Acetone gives 38% of methyl ethyl ketone and 33% of isobutylene oxide.



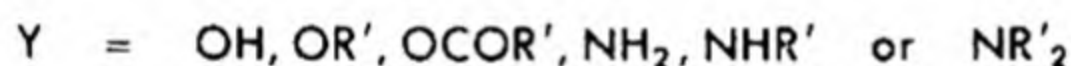
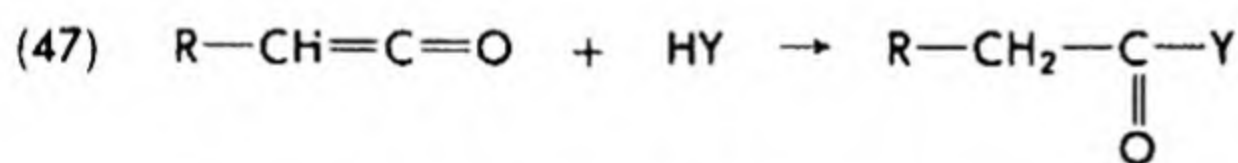
The reaction is particularly useful for ring expansion of cyclic ketones. For example, cyclohexanone gives a 63% yield of cycloheptanone and the latter can be converted in similar yield to cyclooctanone.



The *Wolff rearrangement* (eq. 46), one step in the *Arndt-Eistert synthesis* by which a carboxylic acid is increased in chain length by one carbon atom, (eqs. 45–47) is another reaction which may involve carbene formation. The ketene produced may be isolated or may be formed in a protic medium which will react by addition to the ketene to give an acid, ester, anhydride, or amide.



(order of electron transfers unknown)

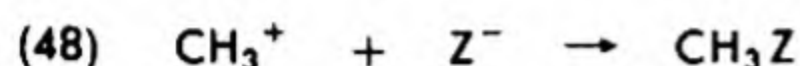


Thus *m*-nitrobenzoic acid is converted to *m*-nitrophenylacetic acid in 65% yield.

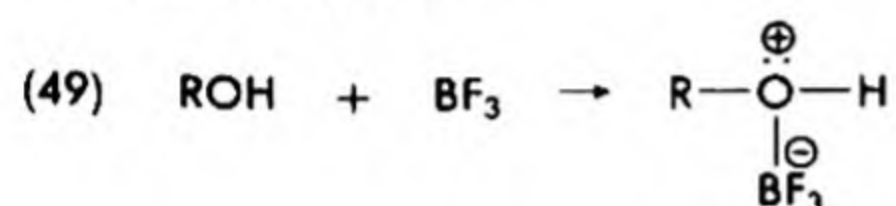


C. Alkylation Reactions

Diazomethane provides one of the cleanest methods for the methylation of acidic compounds. The reaction is quite general and works even with highly hindered compounds which cannot be methylated by methyl sulfate or methyl iodide. Were it not for the inconvenience and hazards inherent in using diazomethane, this reagent might well displace all others for the methylation of costly substrates. Since diazomethane methylations occur with acids or are acid-catalyzed, methanediazonium ion is probably an intermediate in the reaction (eq. 45). Whether the ion pair formed in this reaction collapses to give nitrogen and product (eq. 46) or involves first loss of nitrogen to give a methyl cation (eq. 47) is not known, although for some substituted diazoalkanes the latter path has been demonstrated.



Diazomethane (as well as other diazoalkanes) requires protonation for reaction to occur. Thus, methylation occurs normally only with organic acids and phenols, but not with alcohols. Alkylation of alcohols, however, may be catalyzed by boron trifluoride. This reagent transforms alcohols into strong acids (eq. 49) which are now able to protonate diazomethane (eq. 45).

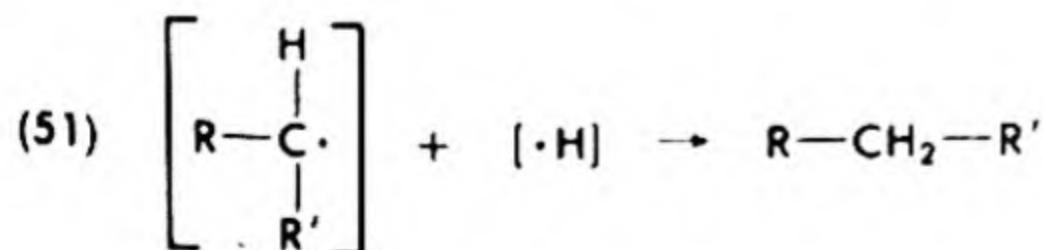
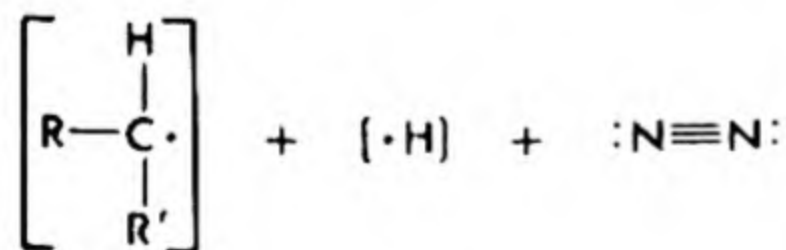
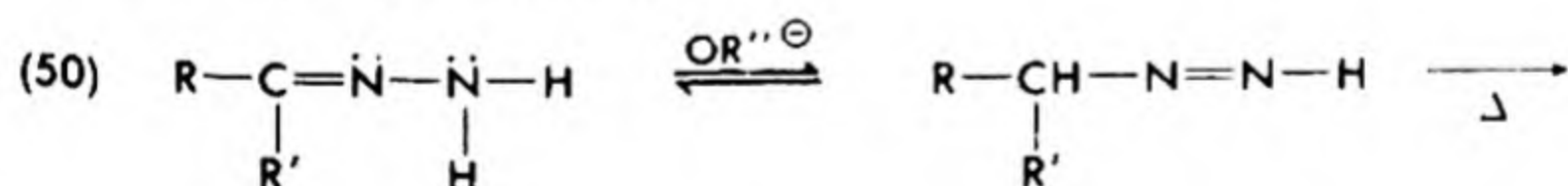


24-4 OTHER RELATED ELIMINATIONS OF NITROGEN. THE WOLFF-KISCHNER REDUCTION

The hydrazone of a ketone or aldehyde can be converted to a hydrocarbon by treatment with a strong base at high temperatures and under anhydrous conditions.

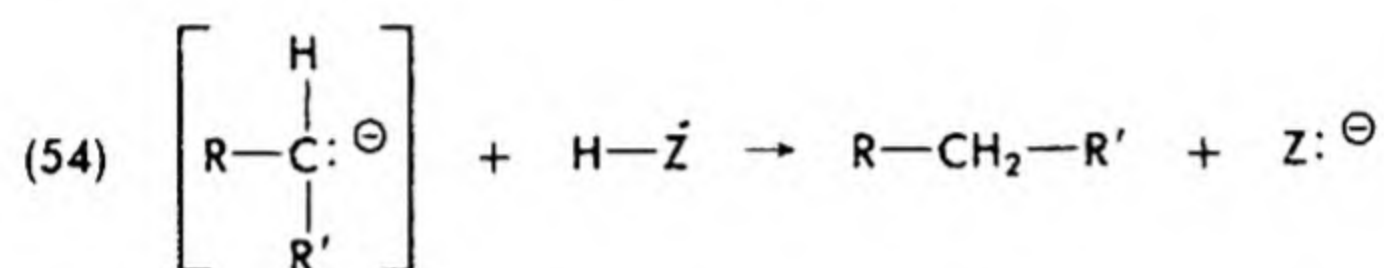
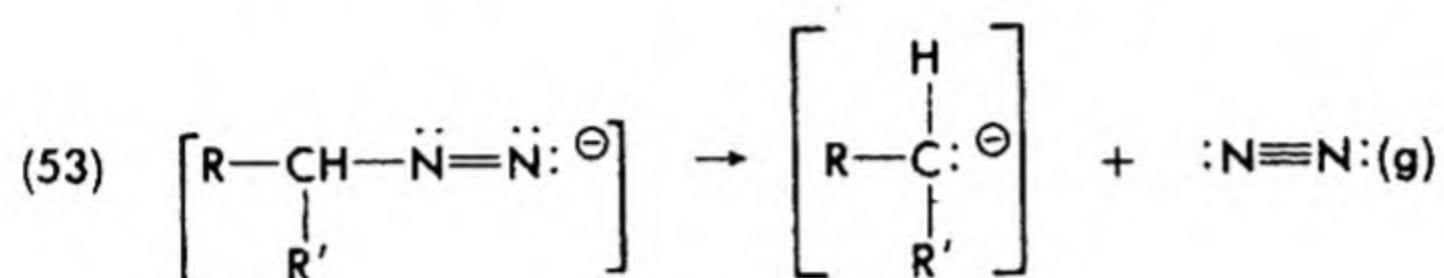
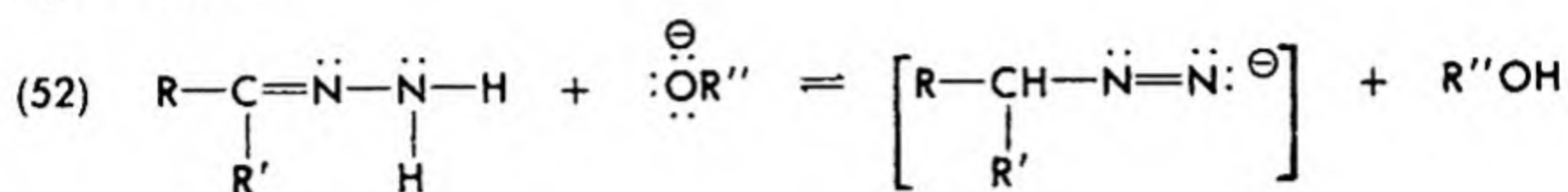
A. Reaction Mechanisms

Studies of reaction rates have indicated that the rate depends on two slow steps. Either of two mechanisms may agree with the data so far available. In eqs. (50) and (51) the base catalyzes tautomerization of the hydrazone, which then eliminates a nitrogen molecule. The resulting free radicals rapidly recombine.



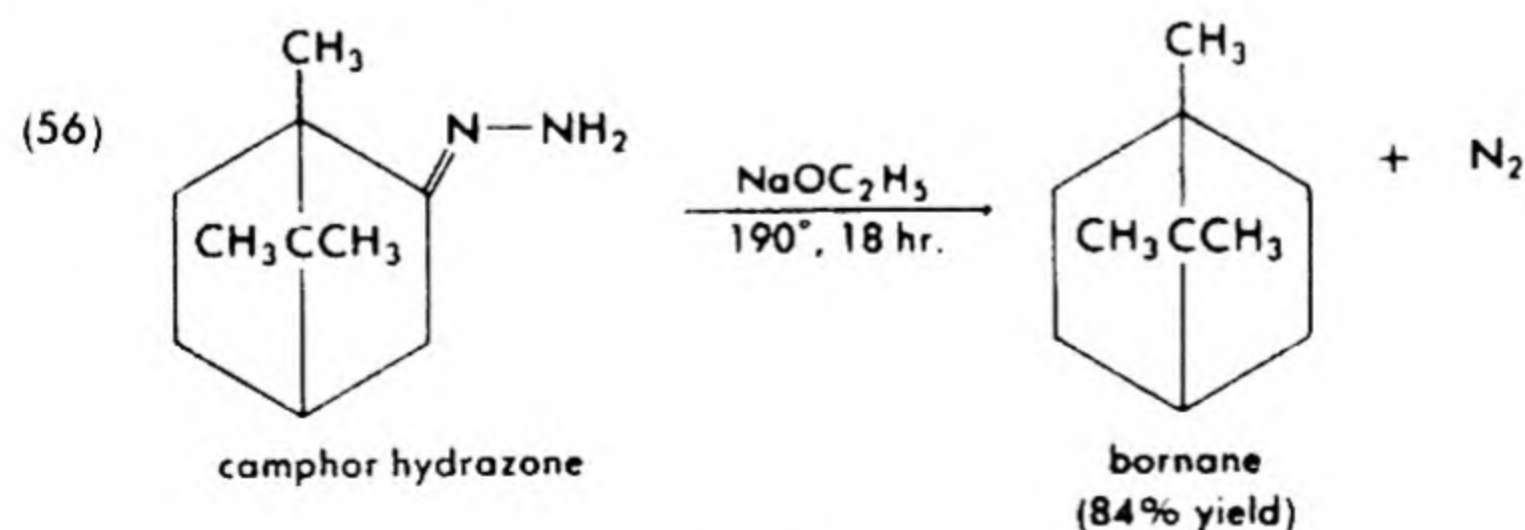
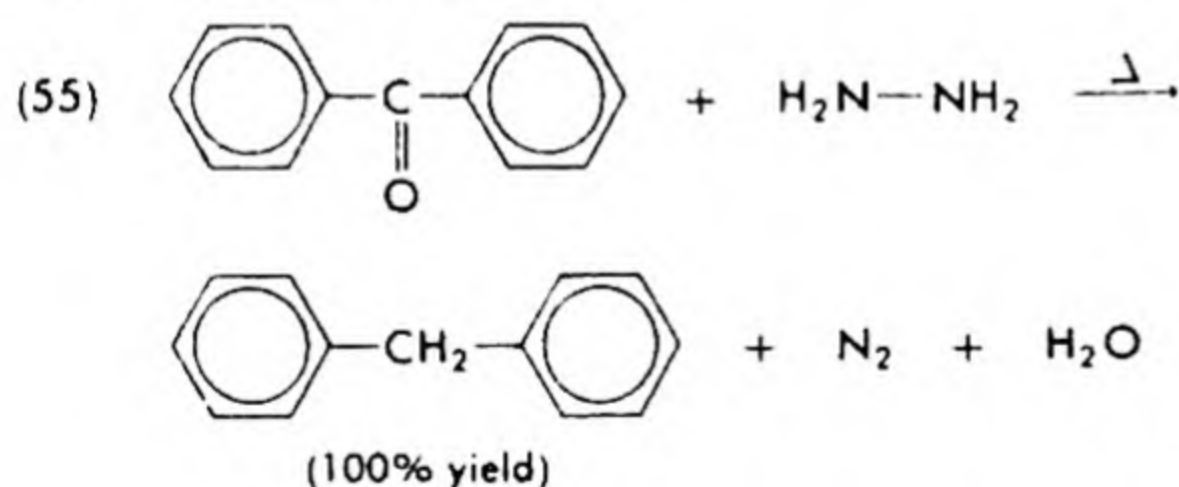
Alternatively, the base may remove a hydrogen ion from the hydrazone, after which heterolytic, rather than homolytic, cleavage may occur. The

carbanion formed quickly removes a hydrogen ion from the next molecule of acid, which may be moisture or alcohol present in traces, or more hydrazone.



B. Representative Reactions

Some compounds, like benzophenone hydrazone, merely require heating with excess hydrazine hydrate. Others, such as camphor hydrazone, require heating for long times at temperatures as high as 200° with sodium or potassium alkoxides. Of the basic catalysts, potassium *t*-butoxide in dimethyl sulfoxide is considerably more effective than the more often used dry sodium ethoxide.

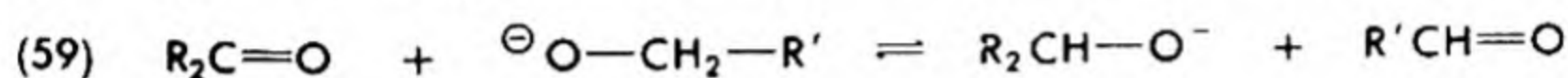
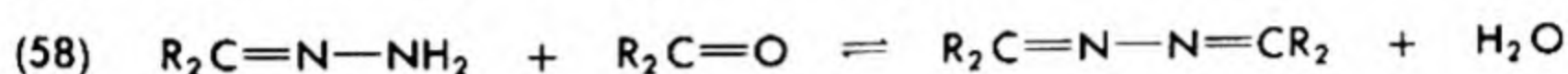
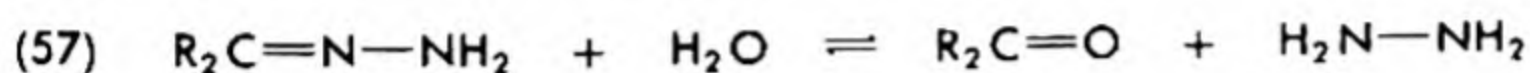


Applicability of the Wolff-Kishner method is quite broad. Most double bonds and functions other than carbonyl are not affected, as long as they

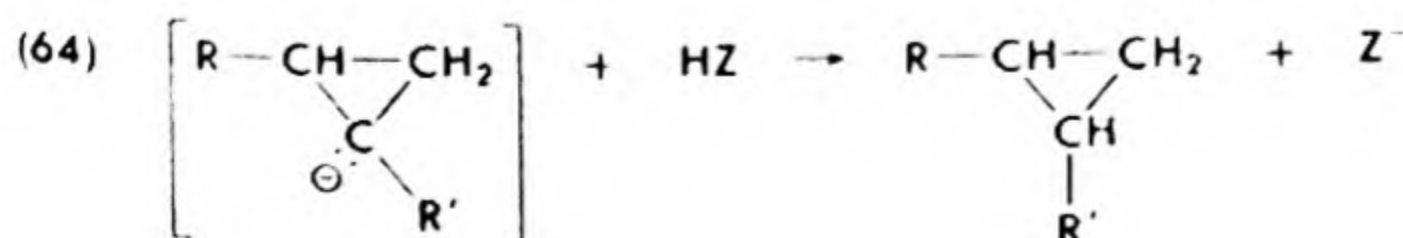
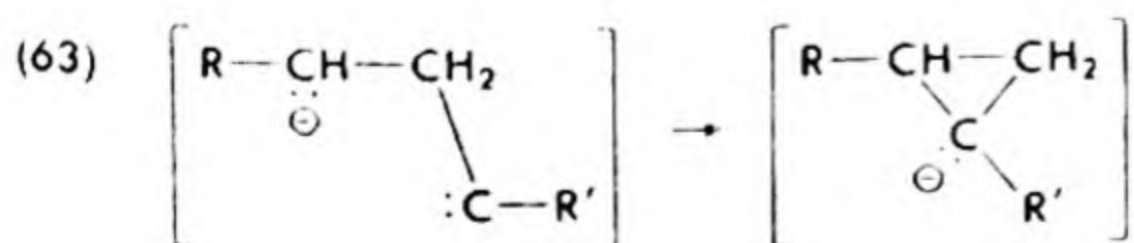
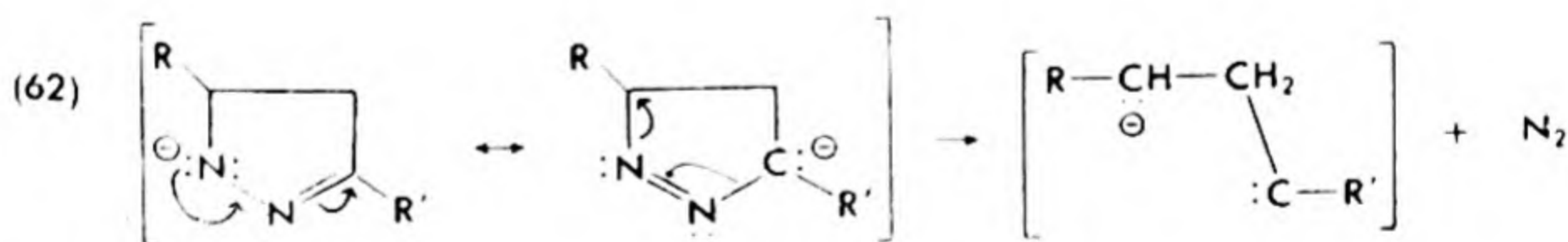
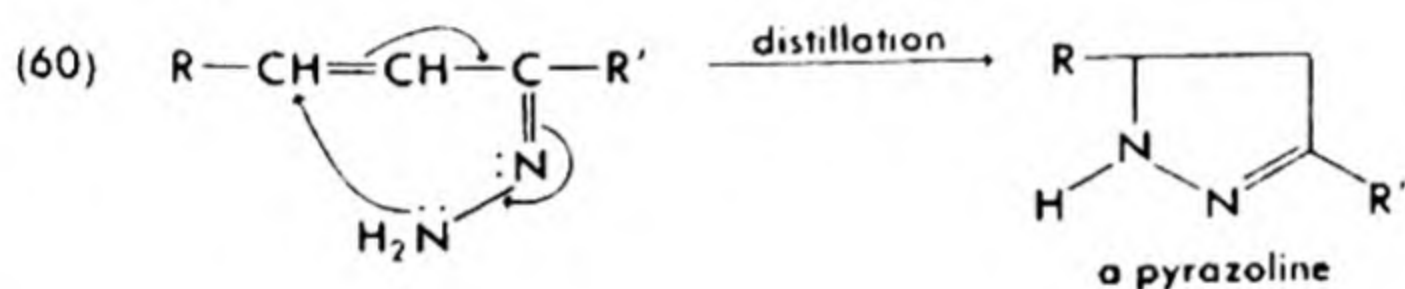
are not sensitive to strong base. Compounds insoluble in water are readily reduced by this method. The reaction does not seem to be subject to steric hindrance.

C. Side Reactions

Three major side reactions can occur in the reduction. Two of these are readily avoided by rigid exclusion of water. These are azine formation (eq. 58) and reduction to carbinols (eq. 59).



A third side reaction, characteristic of conjugated enones, has become a synthetic tool in its own right. Heating the hydrazone of an α, β -unsaturated ketone gives a pyrazoline which, upon treatment in the usual Wolff-Kishner manner, eliminates nitrogen to form a cyclopropane derivative.



SUPPLEMENTARY READINGS

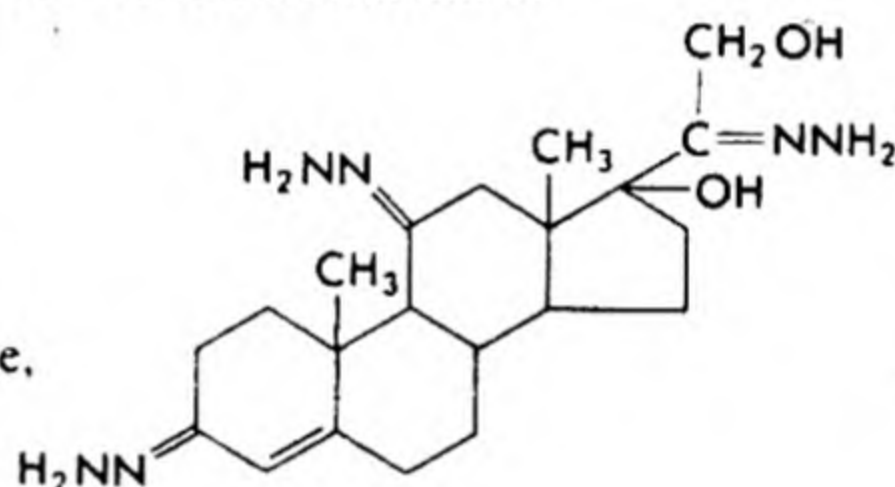
- Bachmann, W. E., and W. S. Struve, "The Arndt-Eistert Synthesis," *Org. Reactions* **1**, 38-62 (1942).
 Gutsche, C. D., "The Reaction of Diazomethane and Its Derivatives with Aldehydes and Ketones," *Org. Reactions* **8**, 364-429 (1954).
 Todd, D., "The Wolff-Kishner Reduction," *Org. Reactions* **4**, 378-422 (1948).
 Zollinger, H., *Azo and Diazo Chemistry*, Interscience, New York (1961).

QUESTIONS AND PROBLEMS

1. Write equations for the reactions that occur between the substances listed together below. Use structural formulas for organic compounds and indicate essential conditions. If more than one product is likely, write an equation for the formation of each.

- a. naphthalene-1-diazonium chloride, cuprous bromide, and hydrobromic acid
- b. 2-methylcyclohexanone and diazomethane

c. cortisone hydrazone,



and potassium

t-butoxide in dimethyl sulfoxide

2. Write the equations for the preparation of the following azo dyes from suitable aromatic amines and coupling agents.

- a. sodium 4-(2-hydroxy-1-naphthaleneazo)benzenesulfonate (orange II)
- b. 1-(4-nitrobenzeneazo)-2-naphthol (*para* red)
- c. disodium biphenyl-*p,p'*-bis(3-azo-4-aminonaphthalene-1-sulfonate) (congo red)
- d. sodium 4-hydroxy-3-benzeneazonaphthalene-1-sulfonate (tropaeolin)
- e. 1,3-bis(2,4-diaminobenzeneazo)benzene (Bismarck brown)

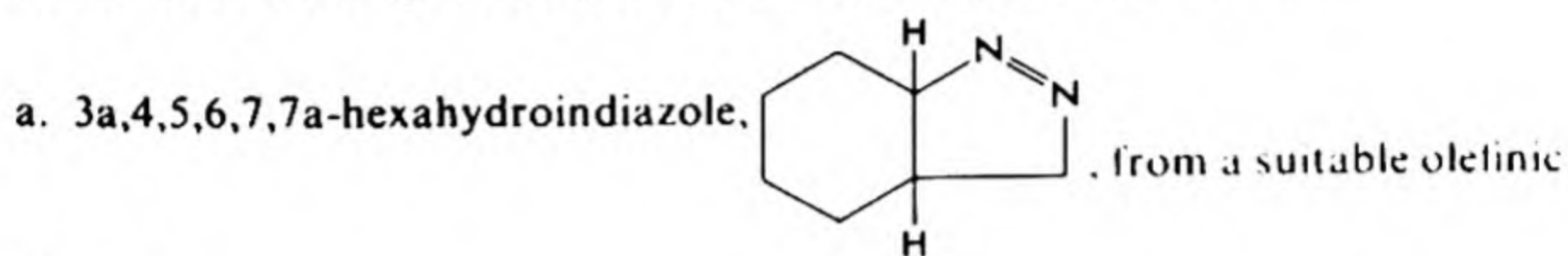
3. Discuss the probable merits of the two ways of preparing 4-aminobenzeneazophenol by coupling.

4. Show how the following syntheses might be performed to give acceptable yields of the desired products. Indicate inorganic reagents and essential conditions. Use structural formulas for organic compounds.

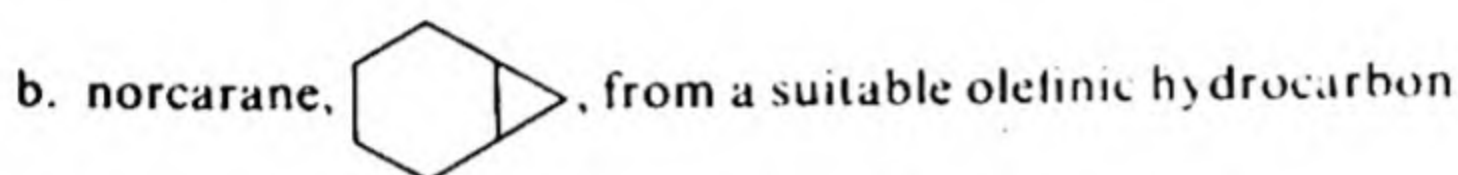
- a. sodium 4-(4-dimethylaminobenzeneazo)benzenesulfonate from aniline, methyl iodide, and inorganic reagents.
- b. Bismarck brown (see Question 2e) from benzene and inorganic reagents
- c. *m*-dichlorobenzene from benzene
- d. *p*-tolunitrile from toluene
- e. *m*-bromophenol from nitrobenzene
- f. *p*-difluorobenzene from benzene

- g. 1,4-naphthalenedicarboxylic acid from naphthalene
- h. *p*-dinitrobenzene from aniline
- i. 4-phenyl-3-butenamide from benzaldehyde, acetic anhydride, and diazomethane
- j. cycloheptanone from cyclohexanone and methylamine

5. Show how the following syntheses might be performed to give acceptable yields of the desired products from diazomethane and other suggested starting materials. Indicate inorganic reagents and essential special conditions.



hydrocarbon



- c. benzene-1,2-diacetic acid from phthaloyl chloride
- d. methyl 2,4,6-trimethylbenzoate from mesitylene
- e. 4-methyl-2,6-di-*t*-butylanisole from phenol, *t*-butyl chloride, and methyl alcohol

6. Show how the following syntheses can be accomplished with the utilization of the Wolff-Kishner reduction.

- | | |
|--|--|
| a. 1,5-diphenylpentane from benzaldehyde and acetone | d. <i>n</i> -propylbenzene from benzene and propionic acid |
| b. 1,1,2-trimethylcyclopropane from acetone | e. ethylcyclopropane from ethyl acetoacetate and ethylene |
| c. 1,2-diphenylcyclopropane from benzaldehyde and acetophenone | |

25

Molecular Rearrangements

25-1 VIOLATIONS OF THE RULE OF MINIMUM STRUCTURAL CHANGE

In most of our study of organic chemistry, we have noted that reactions in which one functional group has been replaced by another proceed in such a way as to maintain the same basic carbon skeleton (rule of minimum structural change). Thus, we observe that ordinarily the new group enters the molecule and becomes attached to the same atom from which the old group leaves. On the other hand, we have pointed out that many reactions are accompanied by skeletal rearrangements and that these are readily understood on mechanistic grounds. The purpose of this chapter is to consider the mechanism of certain rearrangements in detail and to describe others not yet mentioned in earlier chapters.

A. Classification of Molecular Rearrangements

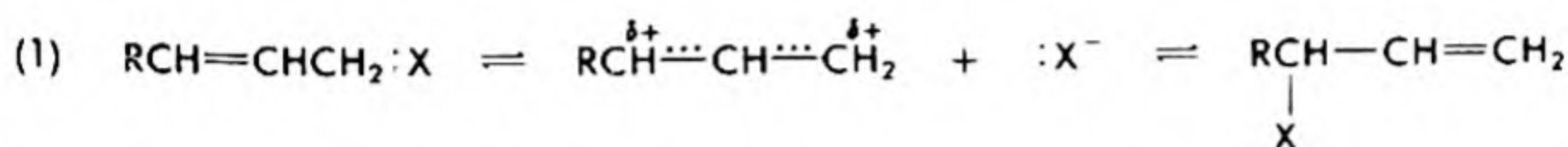
Many molecular rearrangements proceed via stepwise mechanisms. When this is the case, it is possible to classify rearrangements which appear to be quite diverse as being examples of some general mechanistic type. This obviously simplifies the task of understanding these interesting reactions. One class of intermediates may be classified as *electron-deficient*, where species are involved in which one atom has less than an octet of electrons in the valence shell and the driving force for the rearrangement is the completion of the octet. While these may include free radicals, where there are seven electrons in the valence shell of one atom, free-radical rearrangements (see §26-5) are not very important and will therefore not be discussed here. We shall limit the discussion in this classification to rearrangements involving intermediates with atoms having only six electrons in the valence shell.

A second class of rearrangements involves intermediates in which one atom has an unshared electron pair with which it conducts an internal displacement reaction. These we call *electron-rich* rearrangements. Cer-

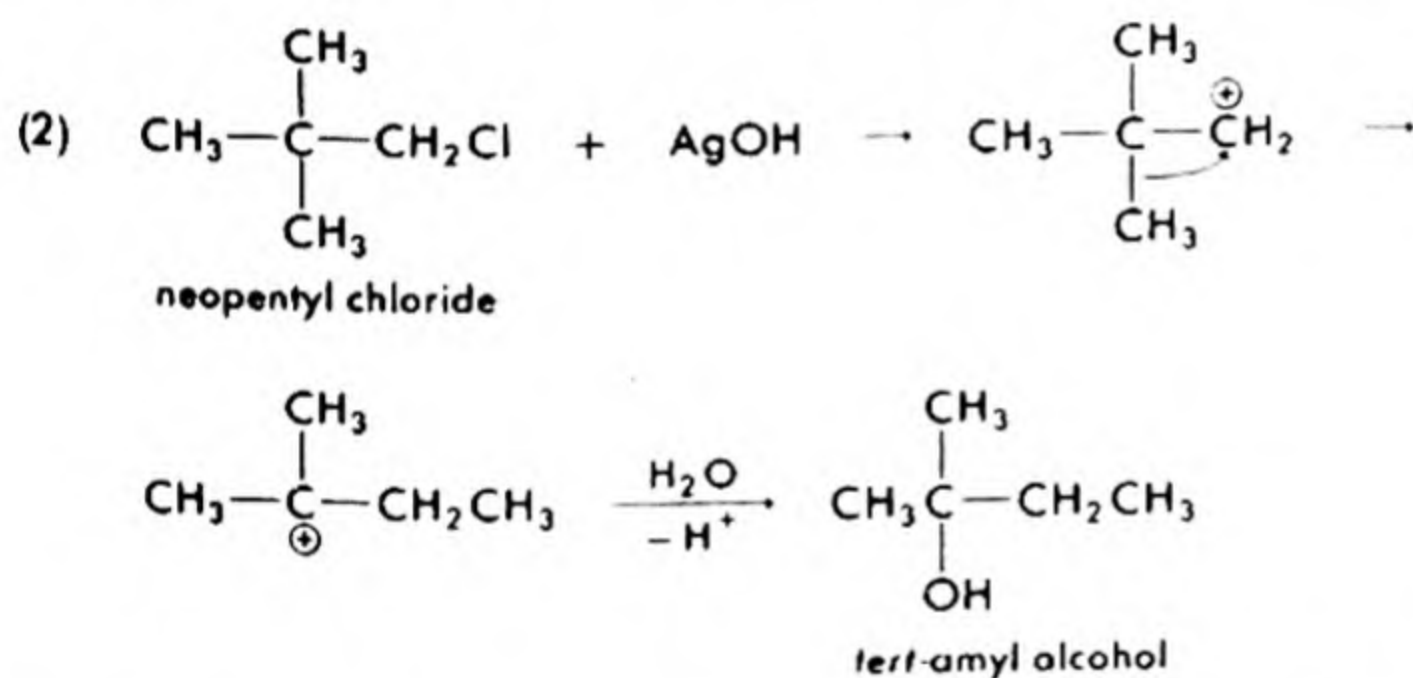
tain other rearrangements have no intermediates (or are of uncertain mechanism) and are therefore not readily classified.

25-2 REARRANGEMENTS INVOLVING ELECTRON-DEFICIENT INTERMEDIATES. GENERAL CONCEPTS

Rearrangements involving electron-deficient intermediates have already been considered in a variety of portions of this text. Included in this class are allylic rearrangements (eq. 1), which have been discussed in detail in §12-1B(5), where the intermediate is an allylic hybrid cation.



The rearrangements observed in carbonium ion displacement reactions, for example, the formation of *tert*-amyl alcohol from neopentyl chloride (eq. 2), have also been discussed at length (§12-2D(1)). In such processes



an electron pair plus the atom or group to which it is bonded migrates from one carbon atom to another. This latter group can be categorized as having a rearrangement as shown in Fig. 25-1A and represents a special class of a more general type represented by Fig. 25-1B. In the more general case a pair of electrons originally bonding group **Z** to atom **A** is transferred (along with **Z**) to the electron-deficient atom **B** (which ordinarily, but not necessarily, is next to **A**) so that the new species has a **B—Z** bond. **Z** may be a hydrogen atom, an alkyl or aryl group, or a nitrogen, oxygen, sulfur, or halogen atom, although the precise details of the transfer may vary with differing **Z** groups. For all of the reactions we will consider, **A** will be a carbon atom, while **B** may be C, N, or O.

A. Carbon to Carbon Migrations

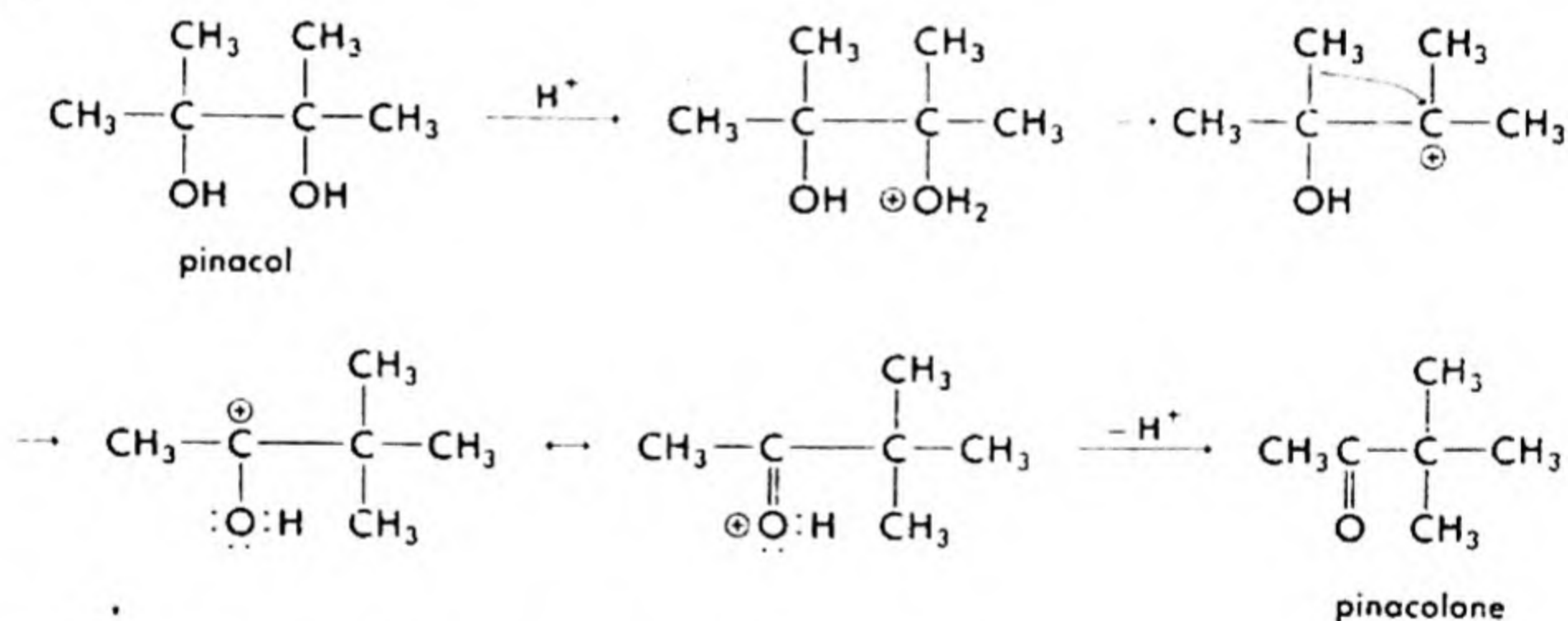
(1) *Carbonium Ion Rearrangements.* The rearrangement step of the Wagner-Meerwein rearrangement involved in the transformation of neo-



Fig. 25-1. (A) A carbonium ion rearrangement. Note that group **Z** migrates with electron pair and that the right-hand carbon atom begins with an electron sextet and ends with an octet, while the opposite is true for the left-hand carbon atom. (B) General case for electron-deficient 1,2-shifts. Note that migration terminus atom **B** originally has six electrons in its valence shell and ends with eight, while migration origin atom **A** loses that electron pair. If no other electron shifts occur, atom **B** loses one positive charge (or gains a negative one) in the rearrangement, while atom **A** gains one positive charge.

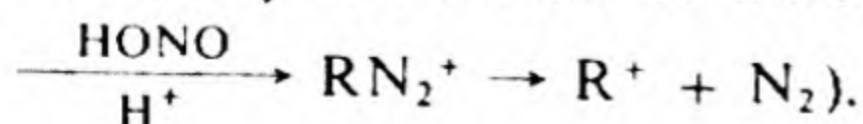
pentyl cation to *tert*-amyl cation (eq. 2) and involved in the pinacol rearrangement (§12-2D(1) and outline 3) are alike in that in each a methide

(3)



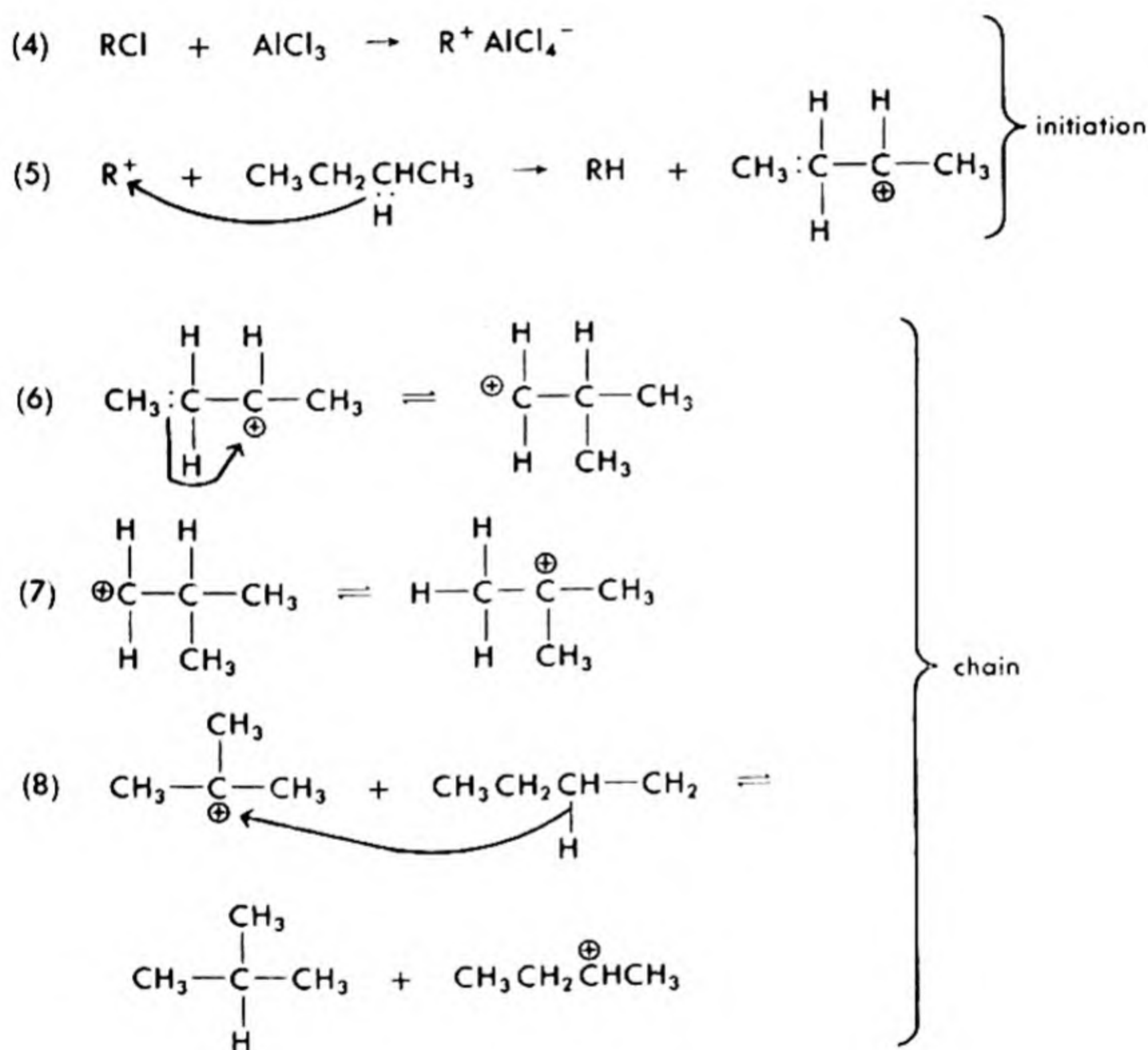
($\text{CH}_3\text{:}$) group migrates from one carbon atom to another, as in Fig. 25-1A. In the case of neopentyl-*tert*-amyl, the driving force of the rearrangement is the conversion of a primary cation to a more stable tertiary ion, while in the second case a more stable ketone conjugate acid is formed.

The group whose departure leaves the carbon atom electron-deficient may be any of those ordinarily considered in displacement reactions (§12-1A(2)). For example, the rearranging carbonium ion may be formed by loss of water, halide ion, toluenesulfonate ion, or nitrogen formed by the action of nitrous acid on an aliphatic amine, RNH_2



While it is true that in the examples mentioned, the less stable ion rearranges to the more stable one, the reverse may be true when ions are formed many times in the course of a reaction and the less stable one is trapped as a less reactive product.

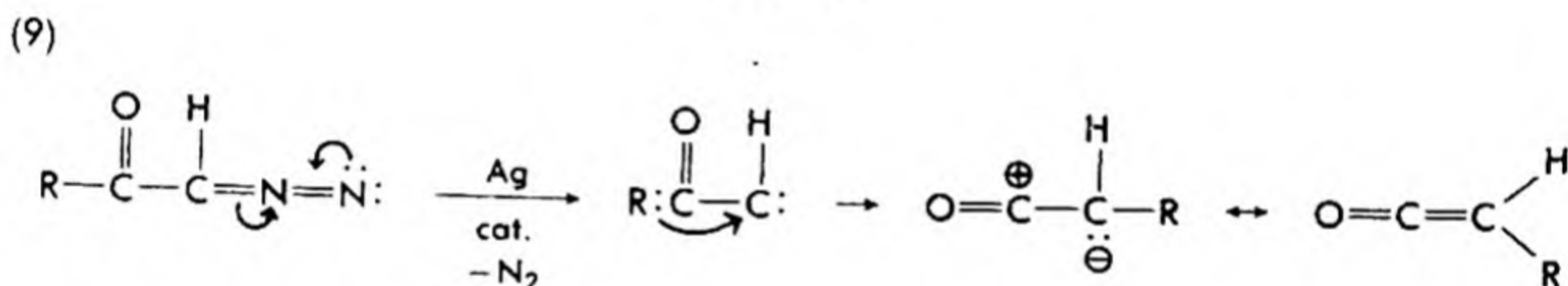
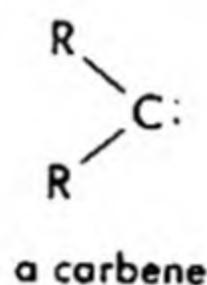
This is observed in the rearrangement of *n*-butane to isobutane, an important process used in the petroleum industry (see §44-1C(5)). This reaction is catalyzed by aluminum chloride and an alkyl halide (or some other carbonium ion source) and gives an equilibrium mixture of almost equal amounts of each isomer. A suggested reaction path is represented in eqs. (4) through (8).



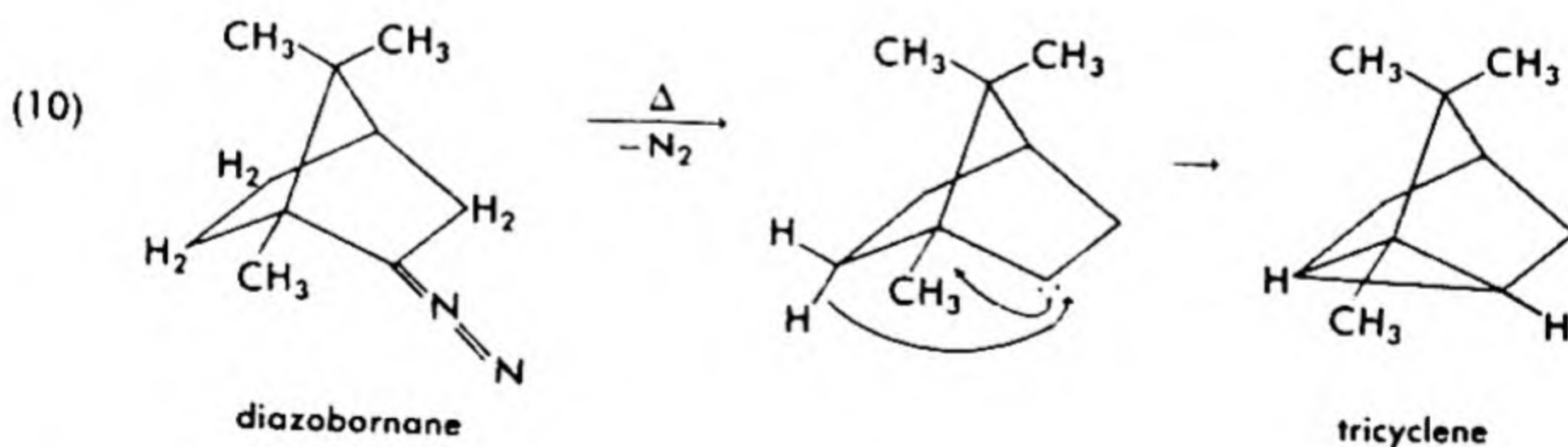
Note that eqs. (6) to (8) constitute a chain in which two endergonic reactions occur. The first is step (6) involving rearrangement from a secondary to a primary cation. The second is step (8) which is an intermolecular hydride transfer (note the correspondence of this reaction to the intramolecular hydride transfers which lead to rearrangement) where a tertiary carbonium ion reacts and a secondary is formed. On the other

hand, step (7) is exergonic. One should remember, however, that in the reverse isomerization, that is, isobutane to *n*-butane, all of the reactions also proceed, but in the reverse fashion. Like all equilibria, thermodynamic factors, rather than kinetic ones, control the position of equilibrium in this reaction, and endergonic steps are readily accommodated so long as they are not prohibitively slow.

(2) *Carbene Rearrangements.* While trivalent carbon atoms with electron sextets are positively charged cations, corresponding bivalent species (carbenes) are neutral. They are, however, quite reactive and among their reactions (see §13-5A) are a variety of rearrangements. Carbenes may be prepared by the decomposition of diazo compounds, and the decomposition of a diazoketone (*Wolff rearrangement*, eq. 9) to a ketene is a step in the important Arndt-Eistert synthesis of carboxylic acids (§24-3B, eqs. 45-47).

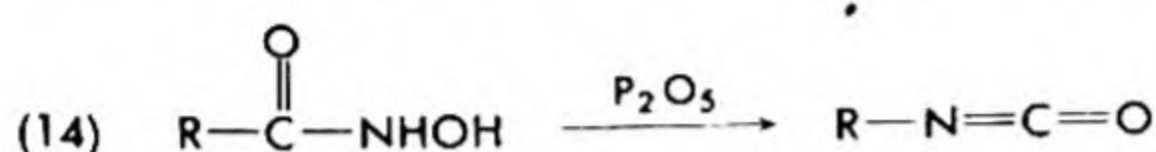
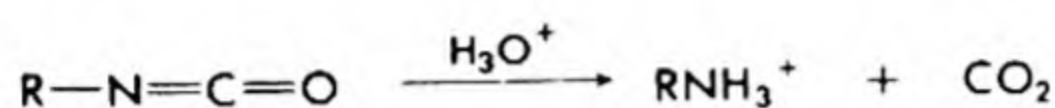
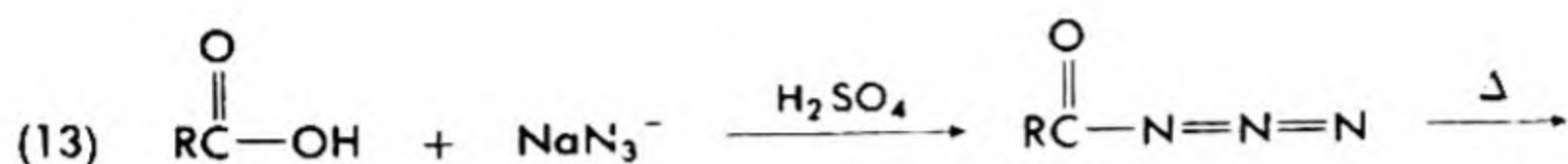
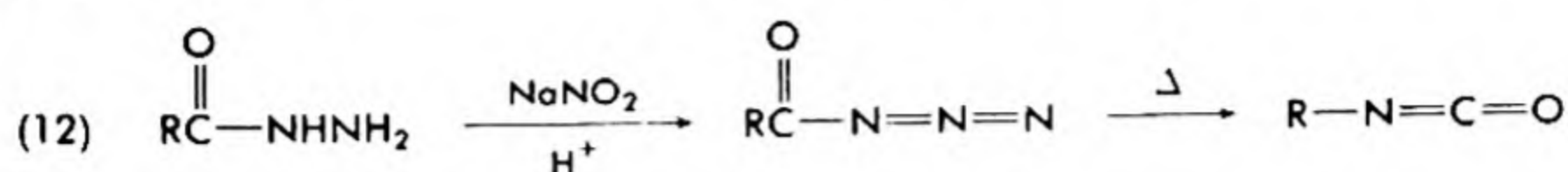
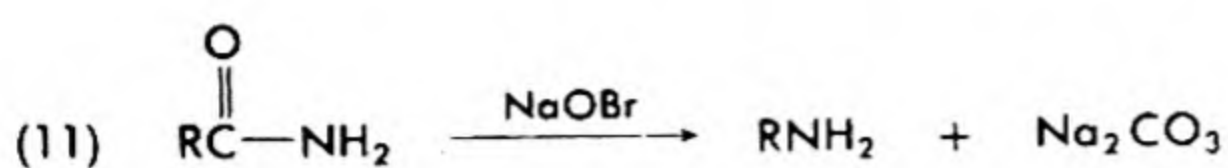


Carbenes may also give insertion reactions into carbon-hydrogen bonds. An example is the preparation of tricyclene from diazobornane (eq. 10).

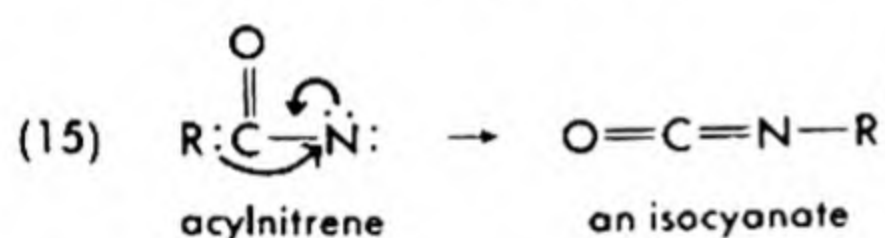


B. Carbon to Nitrogen Migrations

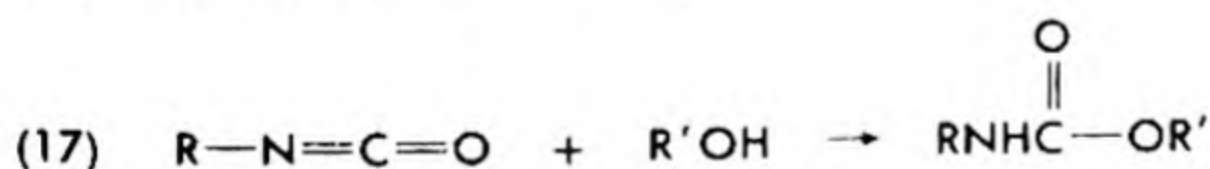
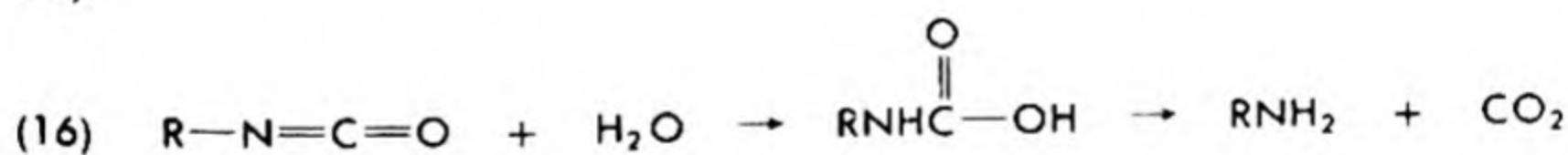
We have already discussed (§13-5B) several reactions in which rearrangement to an electron-deficient nitrogen atom is involved. These include the *Hofmann* (eq. 11), *Curtius* (eq. 12), *Schmidt* (eq. 13), and *Lössen* (eq. 14) rearrangements.



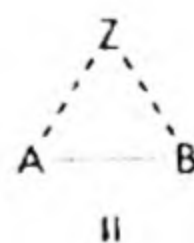
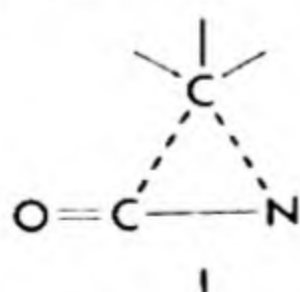
All of these involve the same intermediate, an acylnitrene, which rearranges to an isocyanate (eq. 15). The product which is isolated depends



upon the reactivity of the isocyanate under reaction conditions. When aprotic solvents are used, the isocyanate can be isolated. In water the product is the amine (eq. 16), and in alcohols urethanes are formed (eq. 17).



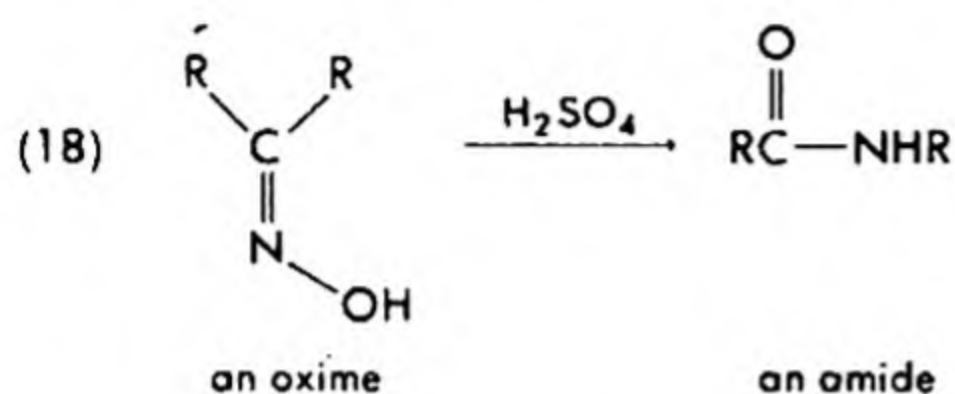
When the R group is optically active, the rearrangement proceeds with net retention of configuration. Thus, these rearrangements proceed in such a fashion that the transfer of R from carbon to nitrogen occurs on the face of the migrating carbon atom. A transition state (or intermediate) of structure I must therefore be involved.



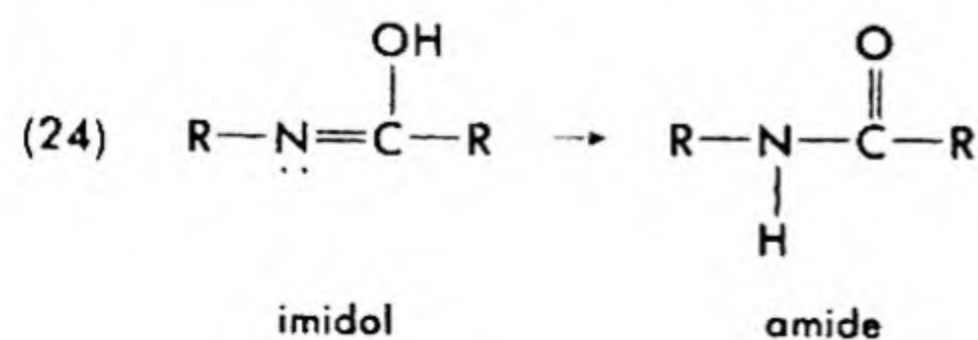
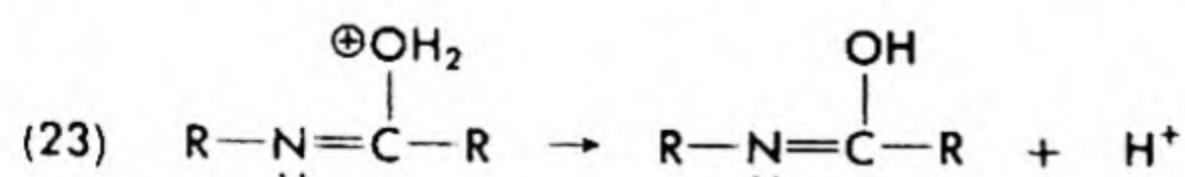
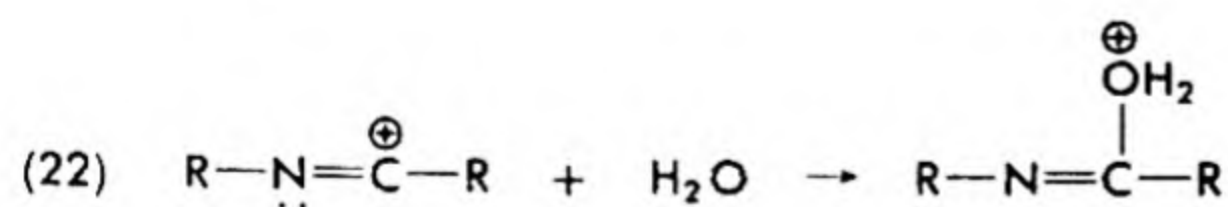
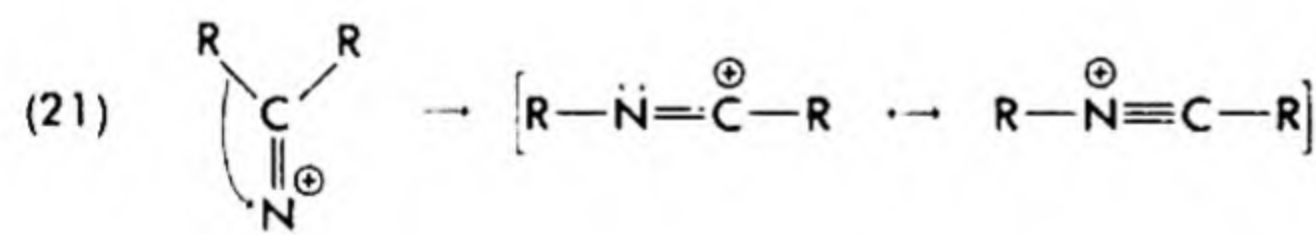
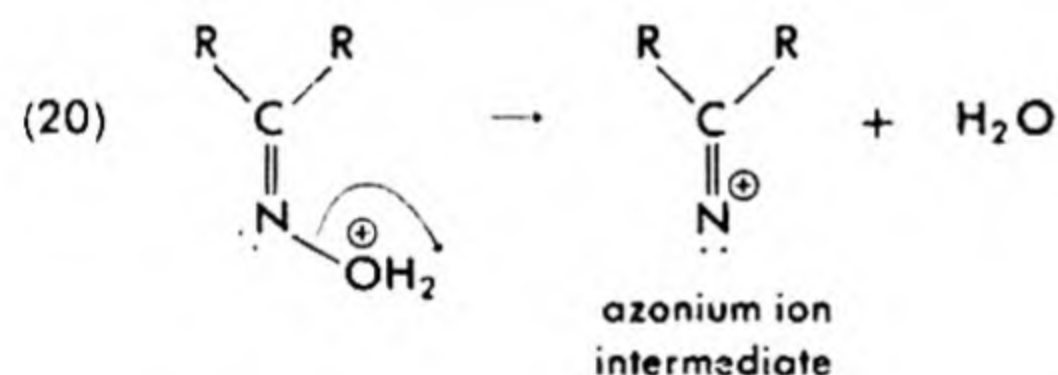
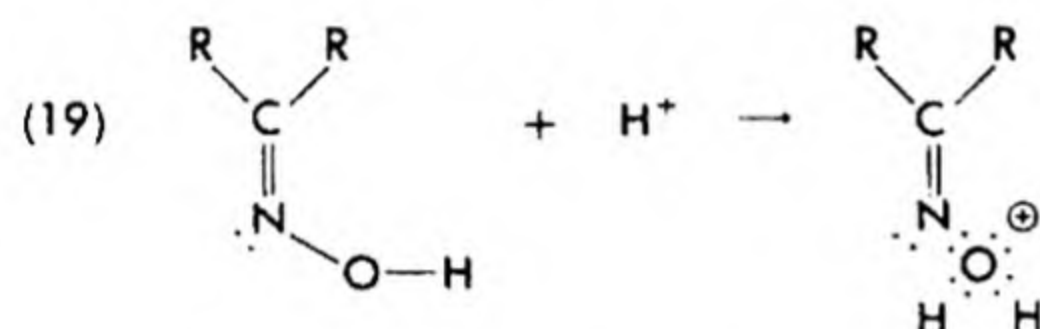
Similar stereochemical results (retention of configuration of migrating group) have been observed in all varieties of electron-deficient rearrange-

ments, and thus the generalized transition state (or intermediate) II appears to be common to all of these.

(1) *The Beckmann Rearrangement.* When an oxime is treated with a strong acid (or with phosphorus pentachloride followed by hydrolysis), it is converted to an amide (eq. 18).



One might reasonably assume that the mechanism given in eqs. (19) through (24) is followed (but see the following section for modification).



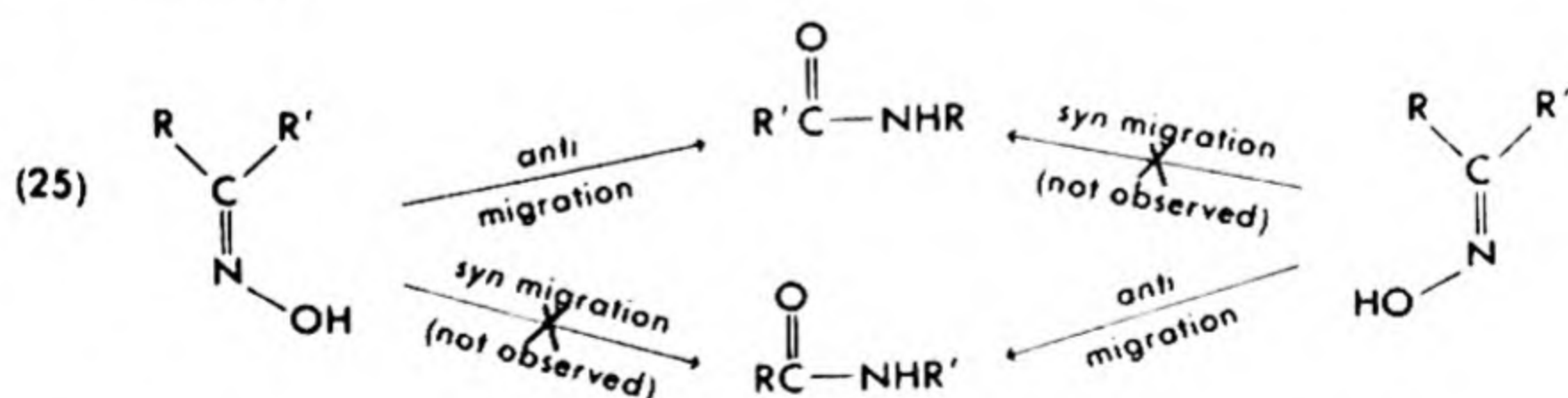
This mechanism is consistent with the observation of ^{18}O exchange when the reaction is conducted in aqueous acid containing an excess of heavy oxygen. This shows that the reaction involves the separation of the oxygen atom from the nitrogen atom *without* concurrent attachment of the oxygen to carbon.

(2) *Stereochemistry of the Beckmann and Other Electron-Deficient Rearrangements* Ketoximes prepared from unsymmetrical ketones may have isomeric structures (i.e., III and IV). The terms *syn* and *anti* are used to describe the relationship of the hydroxyl group to the groups R and R'.

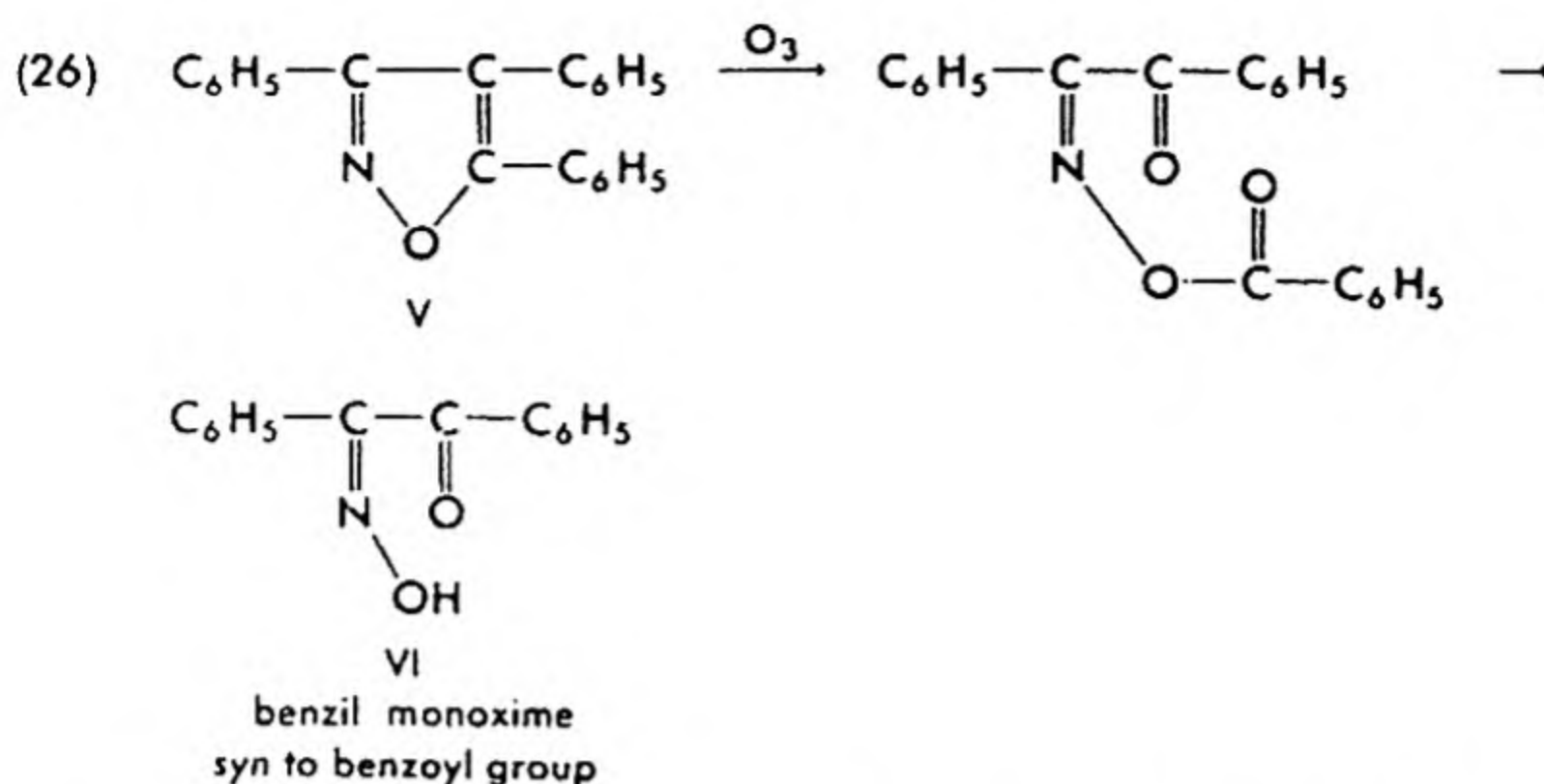


Thus in III, the hydroxyl group is *syn* to R and *anti* to R'; in IV, the reverse is true. The term *syn* is equivalent to *cis* and *anti* to *trans*, which we have used in describing similar geometric isomerism in olefins. The terms *cis* and *trans* may also be used in discussing carbon-nitrogen double-bond isomerism. Such isomers are configurationally stable, and in many cases both oximes can be isolated and studied.

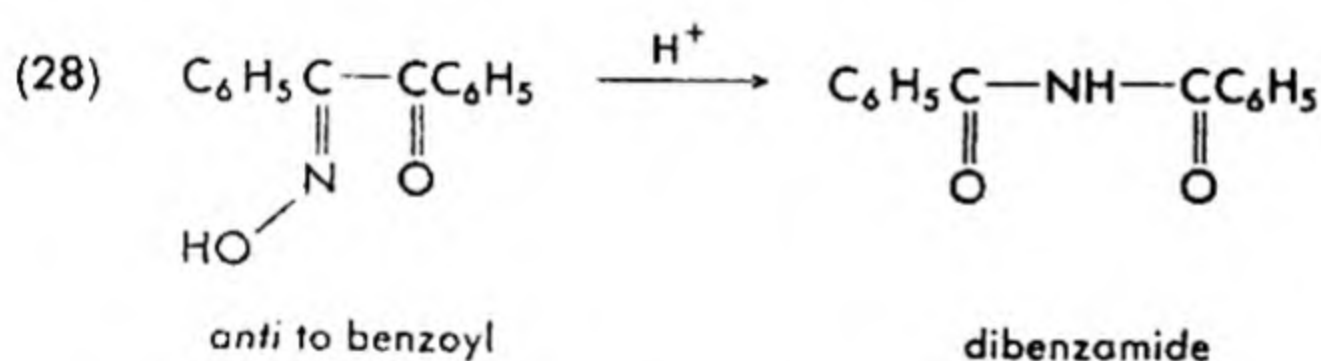
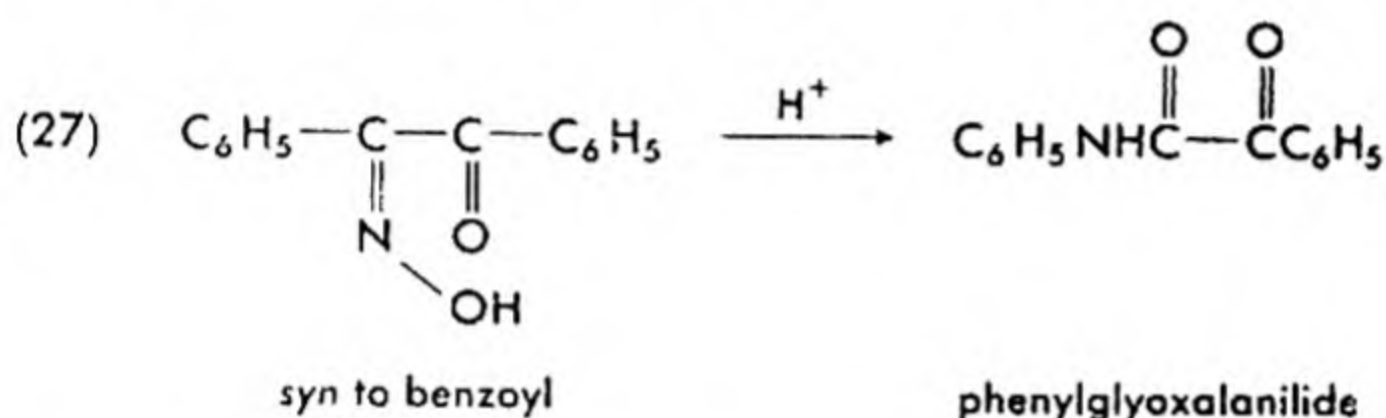
If the mechanism suggested in the previous section were correct, then both members of a pair of isomeric ketoximes would proceed through the same azonium ion intermediate (eq. 20), and both isomers would give the same amide product or an identical mixture of the two possible amide products (outline 25). In fact, however, this is not the case; the reactions are stereospecific and isomeric amides are produced from respective isomeric oximes.



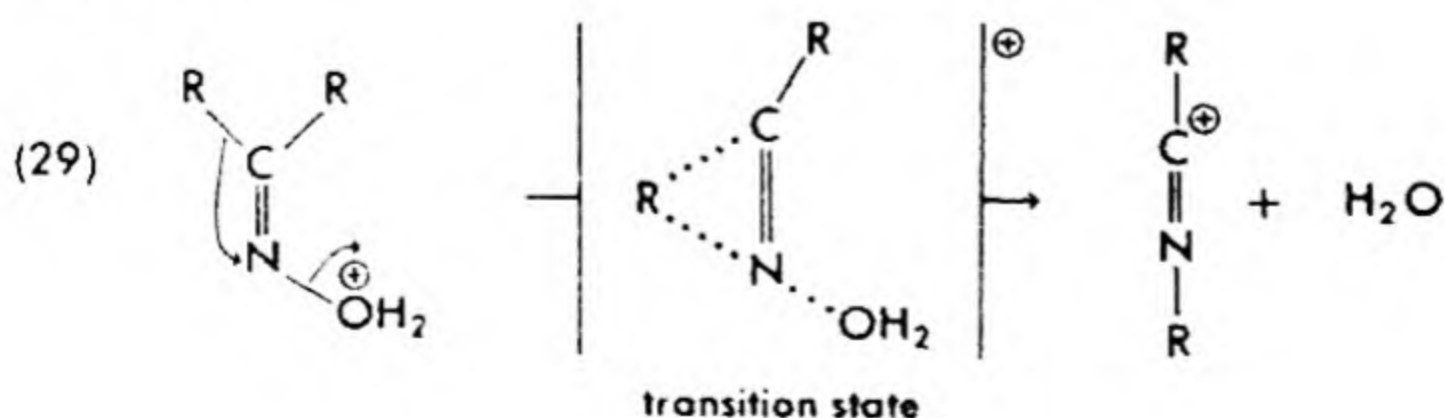
The fact that the migration is *anti* and not *syn* was demonstrated in a classical experiment by Meisenheimer, who set himself the task of preparing an oxime of known configuration. To do this he synthesized one of the monoximes of benzil by ozonolysis of compound V (eq. 26). In the product oxime, the hydroxyl group must be *anti* to the phenyl and *syn* to the benzoyl group. Rearrangement of this oxime gave the anilide of



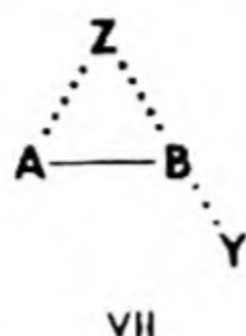
phenylglyoxalic acid (eq. 27), while that of the isomeric oxime, obtained along with VI from benzil and hydroxylamine, gave dibenzamide (eq. 28).



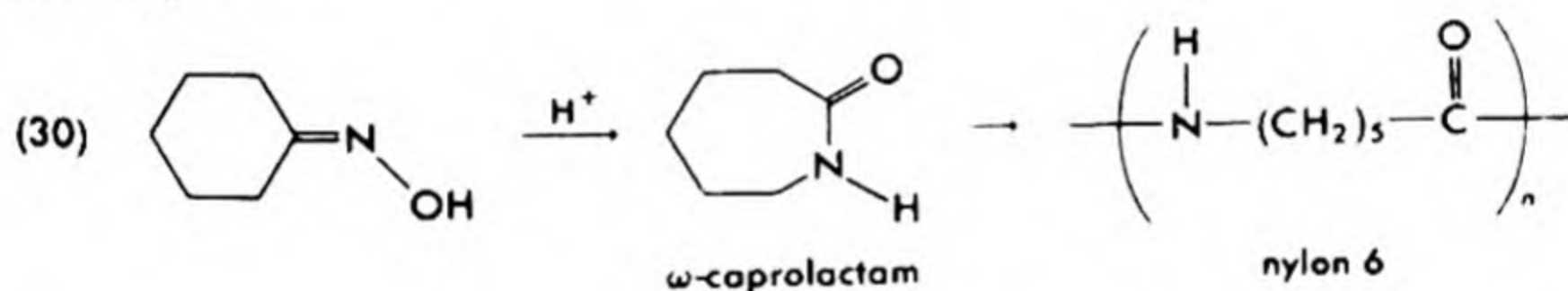
The results clearly show that an intermediate such as the azonium ion (eq. 20) cannot be involved and that any mechanism involving such an intermediate must be incorrect. One can, however, accommodate the stereochemical data, as well as all other data, by assuming that the transformations represented in eqs. (20) and (21) are not separate events but are coalesced into one step. Thus one assumes that the migration of R from carbon to nitrogen is concerted with the heterolysis of the nitrogen-oxygen bond, as in eq. (29). In such a process, then, *anti* migration is required.



Experiments involving not only carbon to nitrogen migrations, but also carbon to carbon migrations have shown that in most, although perhaps not in all, such rearrangements, migration of *anti* groups is the stereospecific result. We therefore generally assume that a transition state of structure VII is involved in such cases.



(3) *Uses of the Beckmann Rearrangement.* As so many other methods are available for the preparation of amides, especially direct methods such as the acylation of amines, the synthetic usefulness of the Beckmann rearrangement is rather limited. However, one example is of considerable industrial importance; it involves the rearrangement of cyclohexanone-oxime to ω -caprolactam (eq. 30). This gives a simple synthesis of a seven-member lactam ring not readily prepared otherwise. Polymerization of ω -caprolactam leads to nylon 6, an industrially important polyamide (see §46-5B).

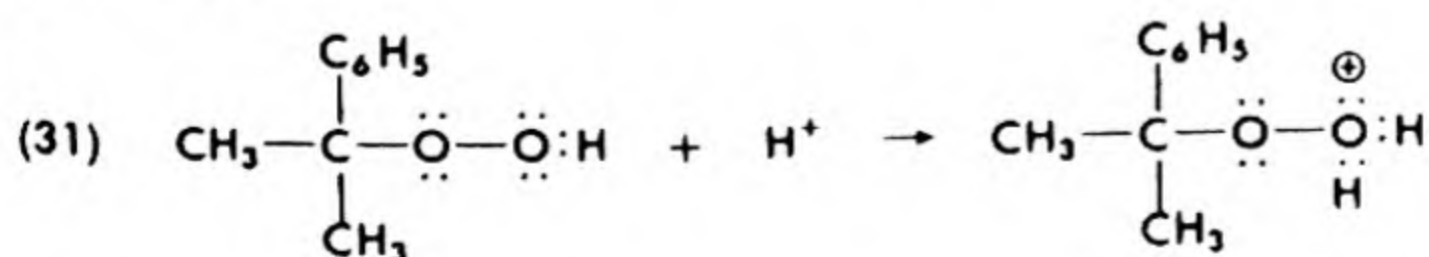


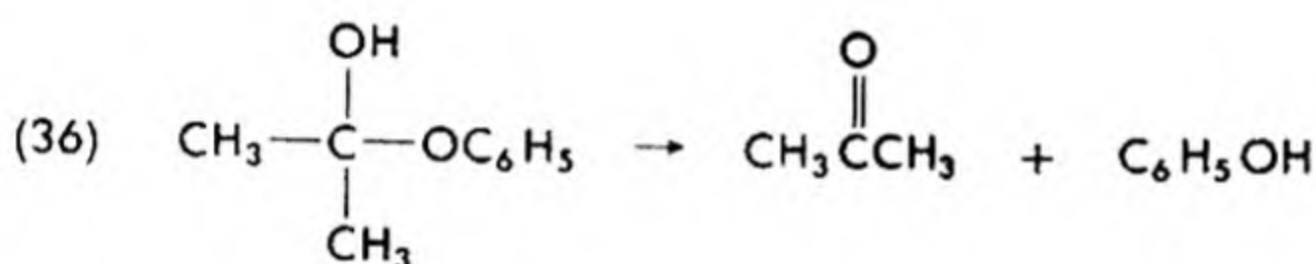
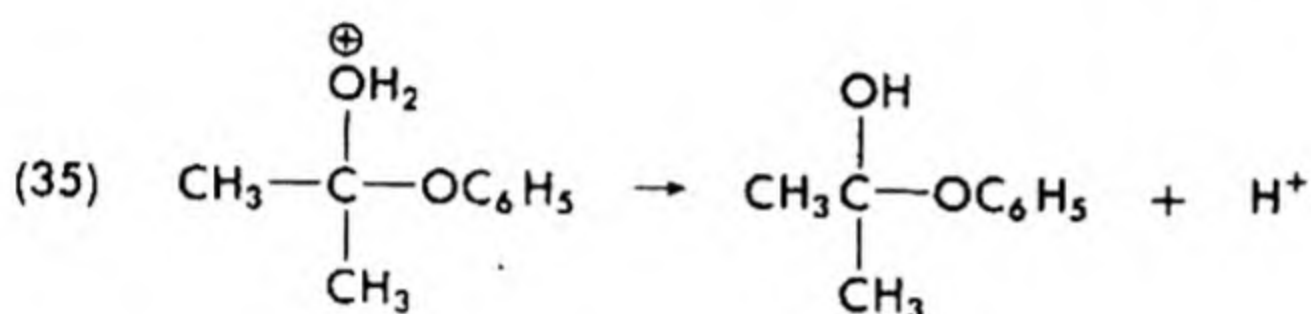
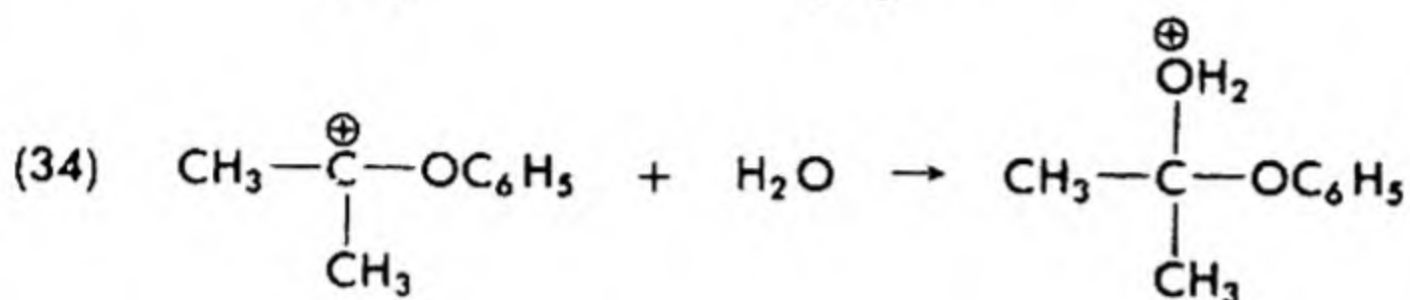
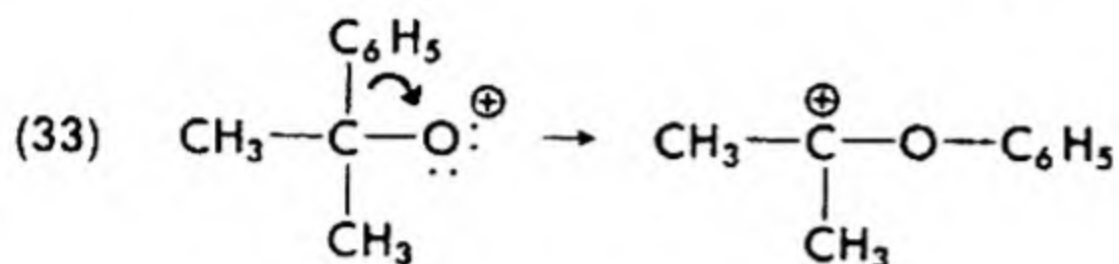
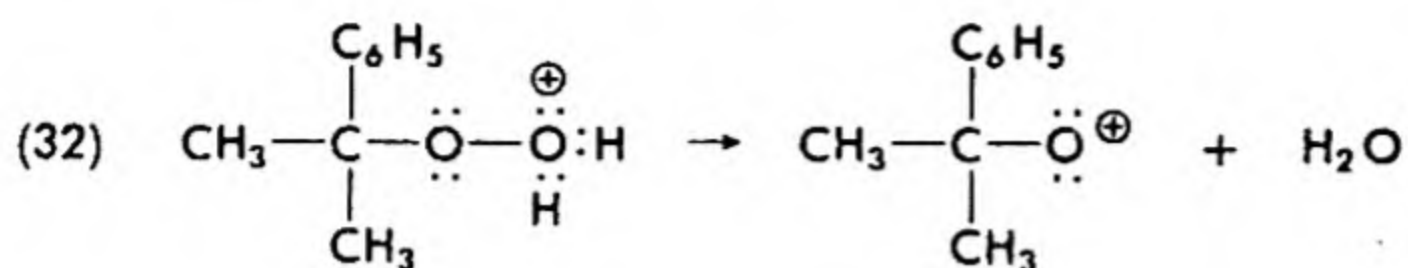
Other medium size ring lactams are also prepared by the Beckmann rearrangement.

C. Carbon to Oxygen Migrations

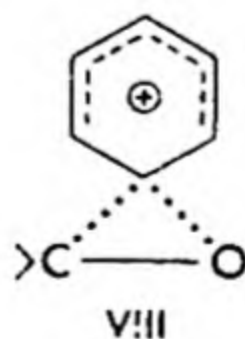
Rearrangement of groups from carbon to electron-deficient oxygen is observed in several interesting and important reactions, of which we shall describe the rearrangement of hydroperoxides and the Baeyer-Villiger oxidation of ketones to esters.

(1) *Rearrangement of Alkyl Hydroperoxides.* When an alkyl hydroperoxide is treated with strong acid, rearrangement to a hemiacetal occurs. The example given is the industrially important production of phenol and acetone from cumene hydroperoxide (for preparation of the latter, see §26-4C(2))

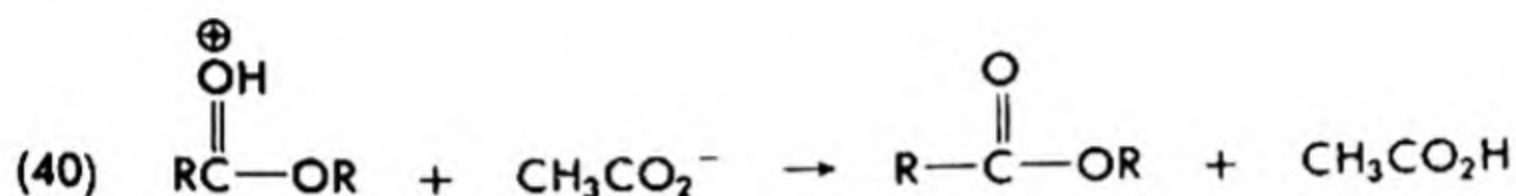
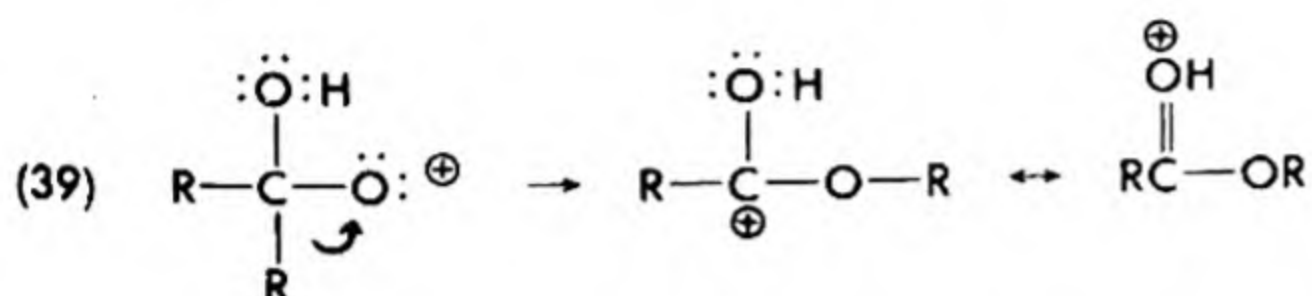
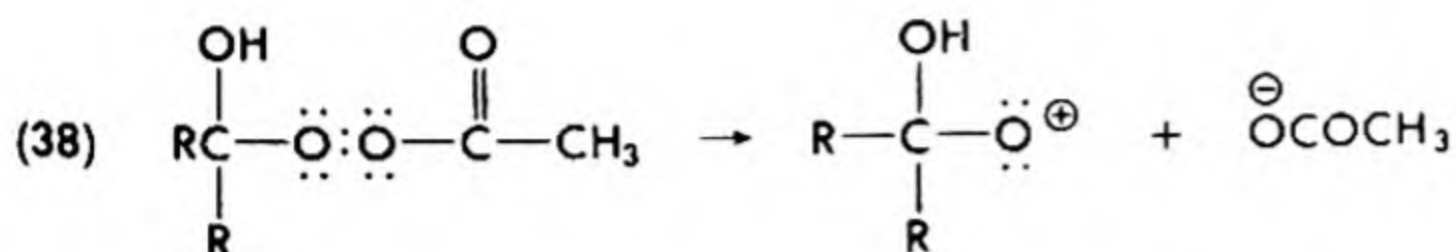
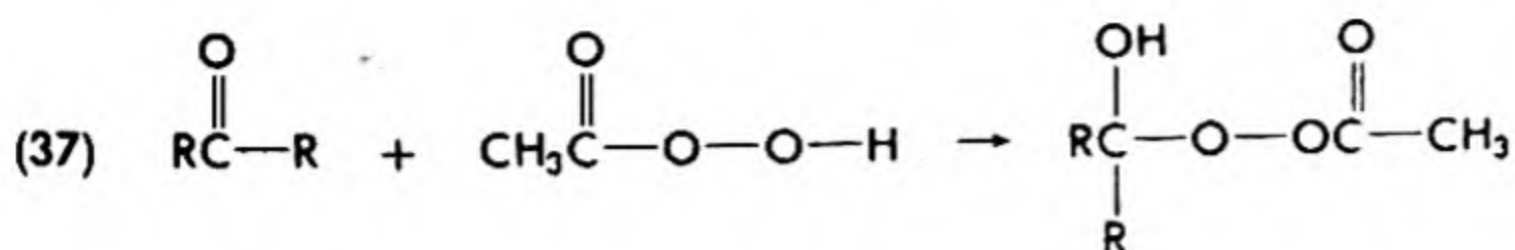




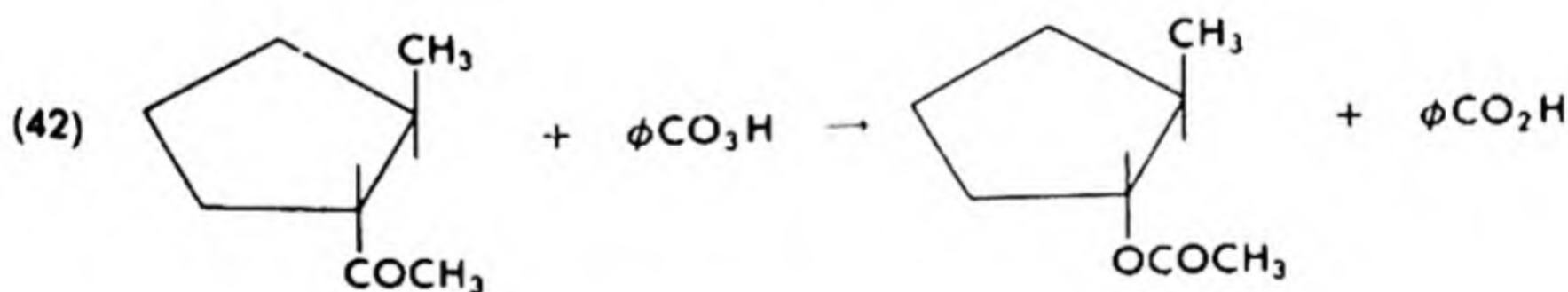
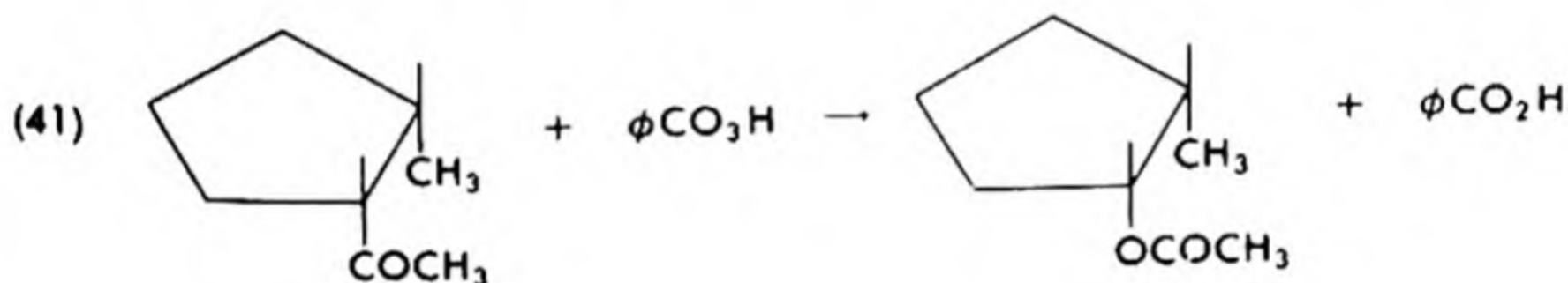
Note that the phenyl group migrates (eq. 33) rather than the methyl group, even though a more stable carbonium ion would result (stabilization by phenyl rather than methyl) if the latter occurred. This preferred migration is explained by the delocalization of the positive charge involved in the transition state (or intermediate) for phenyl migration, VIII. This intermediate is similar to that involved in aromatic electrophilic displacement (Chapter 15), which is very closely related. Aryl groups are observed to migrate more readily than alkyl groups in all (stereochemically permitted) electron-deficient rearrangements.



(2) *The Baeyer-Villiger Reaction.* When a ketone is treated with an organic peracid or with Caro's acid (peroxysulfuric acid, H_2SO_5), it is converted to an ester. The key step (eq. 39) in this reaction is another example of a rearrangement from carbon to electron-deficient oxygen.

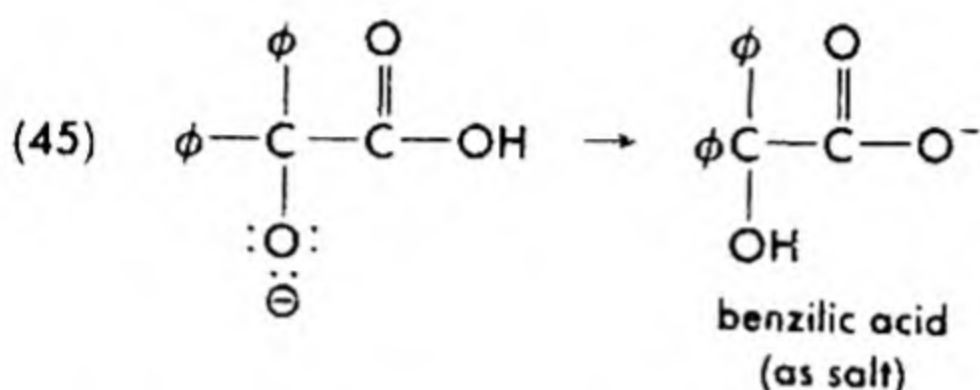
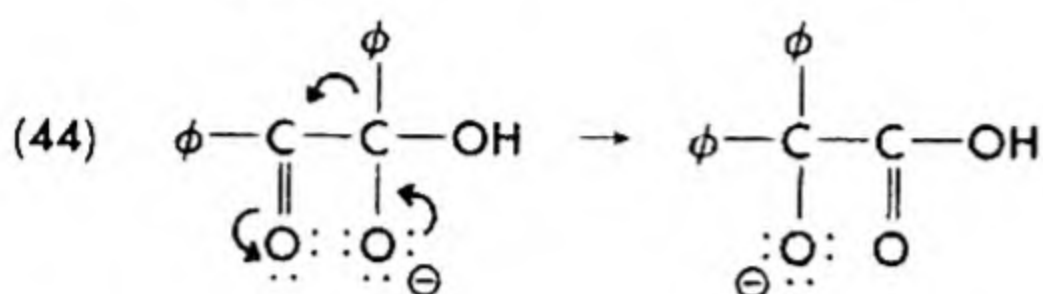
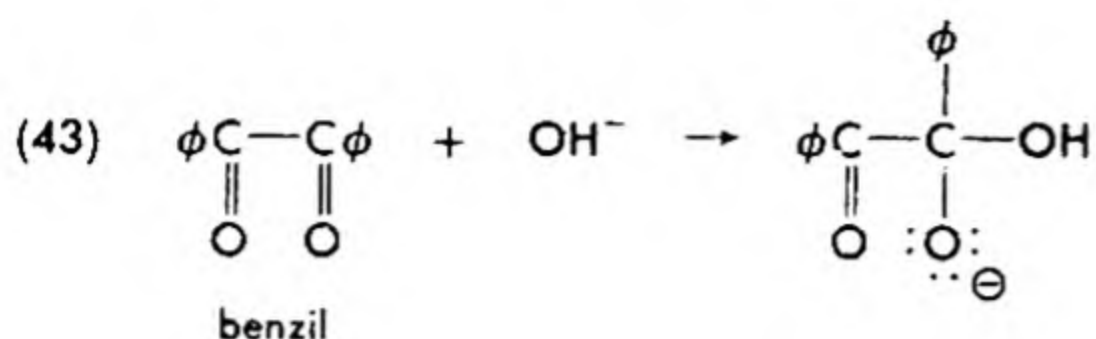


This reaction is of considerable synthetic utility, proceeding normally in about 60% yield. As is the case in most rearrangements, it is stereospecific, with retention in the migrating alkyl group. As seen in the examples given, secondary alkyl groups migrate in preference to primary.



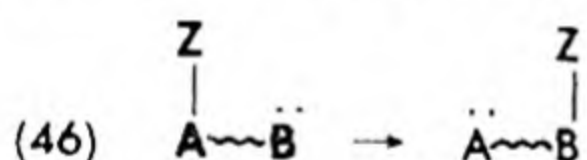
D. The Benzilic Acid Rearrangement

Any benzil-like compound, including the parent benzil, can be rearranged in alkali to form the salt of an hydroxy acid, related to the parent benzilic acid. While this reaction is often considered to be different from the reactions we have discussed above because it is base catalyzed, it is *mechanistically* similar in that an aryl group is transferred to a carbon atom that is sensibly electron deficient, being at the positive end of the strong bond dipole of a carbon-oxygen double bond. The course of the reaction is believed to be the following.



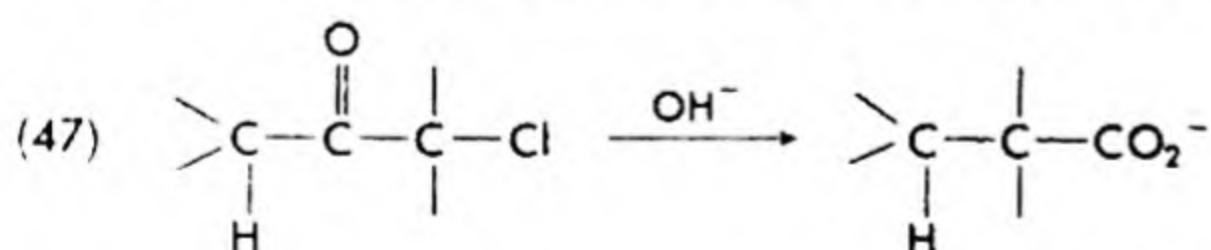
25-3 MIGRATIONS TO ELECTRON-RICH CARBON ATOMS

A variety of organic reactions involve skeletal rearrangements in which a group is transferred without its electron pair. Most of these can be classified as internal displacement reactions (eq. 46), where an unshared electron pair on an atom **B** in one part of a molecule forms the **B—Z** bond, displacing atom **A** and leaving it with the electron pair.

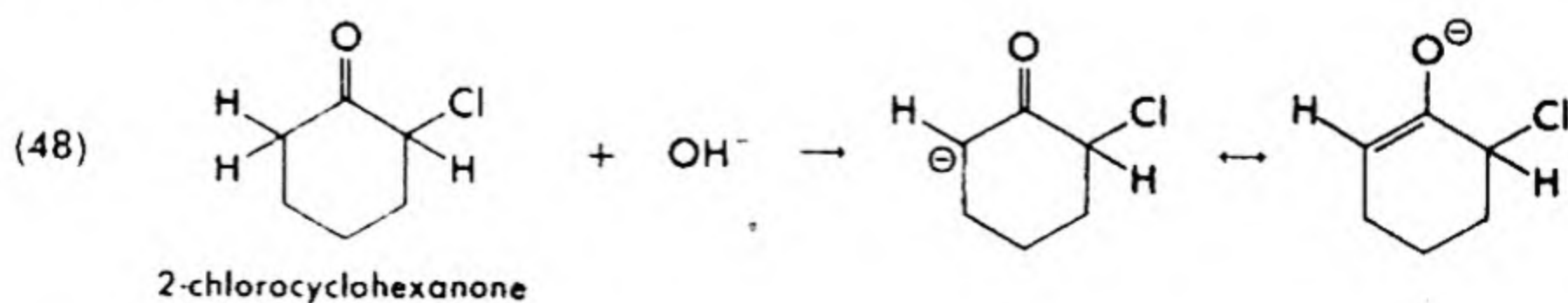


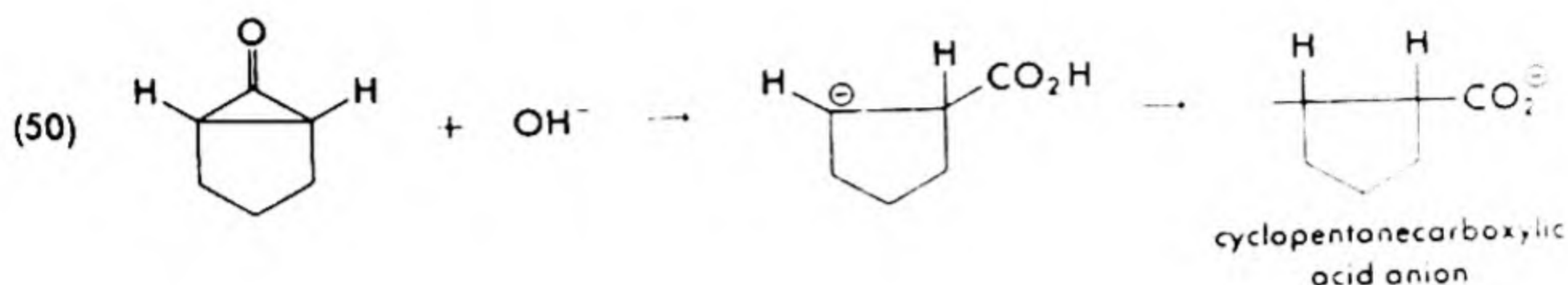
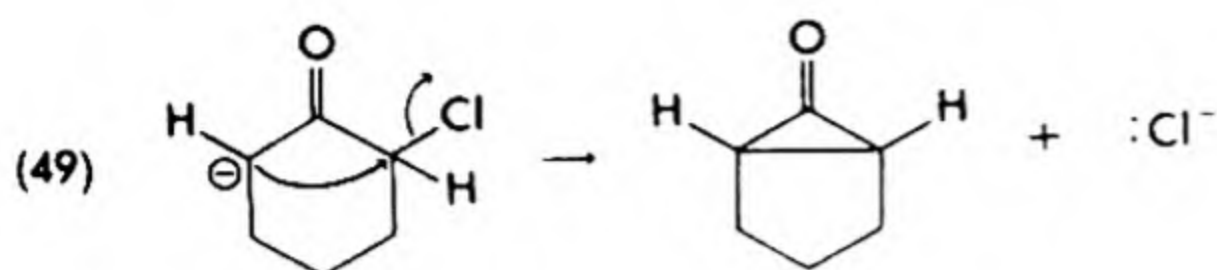
A. The Favorsky Rearrangement

The *Favorsky rearrangement* is an example of a migration to an electron rich carbon atom. This reaction involves the conversion of α -chloro-ketones to salts of carboxylic acids by alkali (eq. 47). Enolate ions and cyclopropanones are suggested as intermediates. An interesting example is seen in the conversion of 2-chlorocyclohexanone to the salt of cyclo-



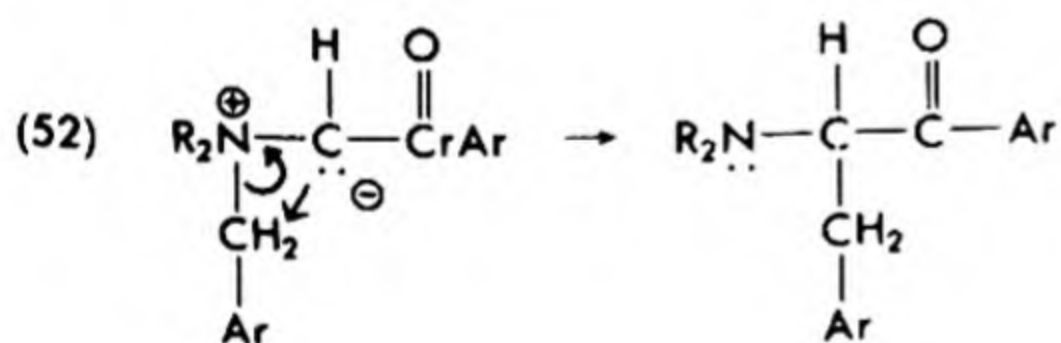
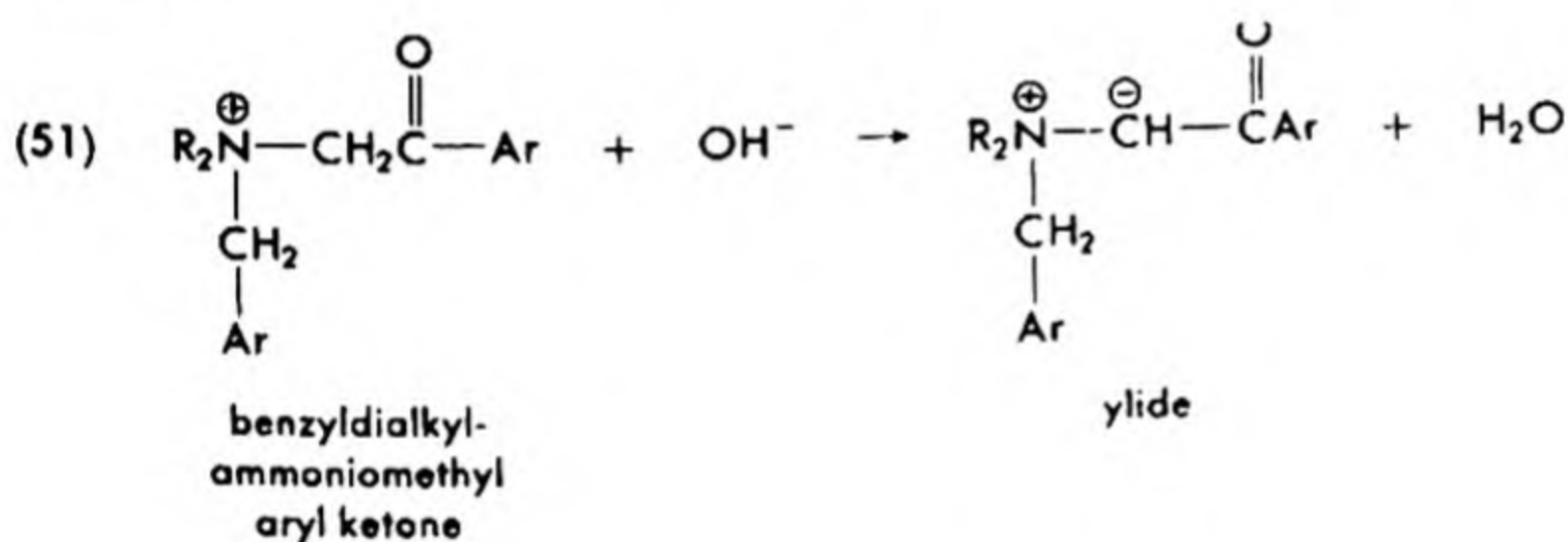
pentanecarboxylic acid. This example and the accepted mechanism are shown in eq. (48).





B. The Stevens Rearrangement

Another such rearrangement occurs in the treatment of benzyldialkylammoniomethyl aryl ketones with alkali. The reaction intermediate in the Stevens rearrangement is a zwitterion or *ylide*. The reaction course is as follows.



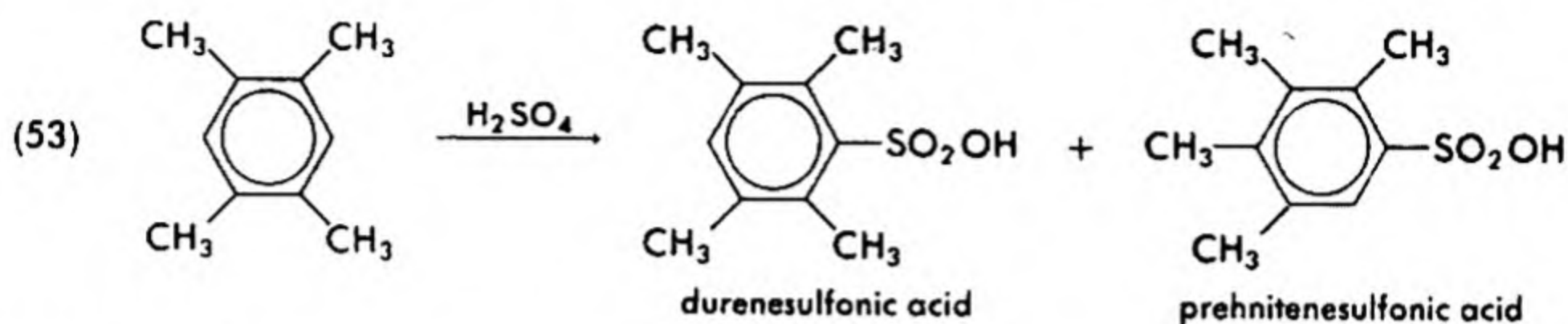
25-4 AROMATIC REARRANGEMENTS

Two classes of rearrangements involving aromatic compounds can be readily classified and discussed separately. One of these involves migrations of substituents from one position on the ring to another. The second involves migration of an atom or group from an atom contiguous to the ring to a position *ortho* or *para* to that atom.

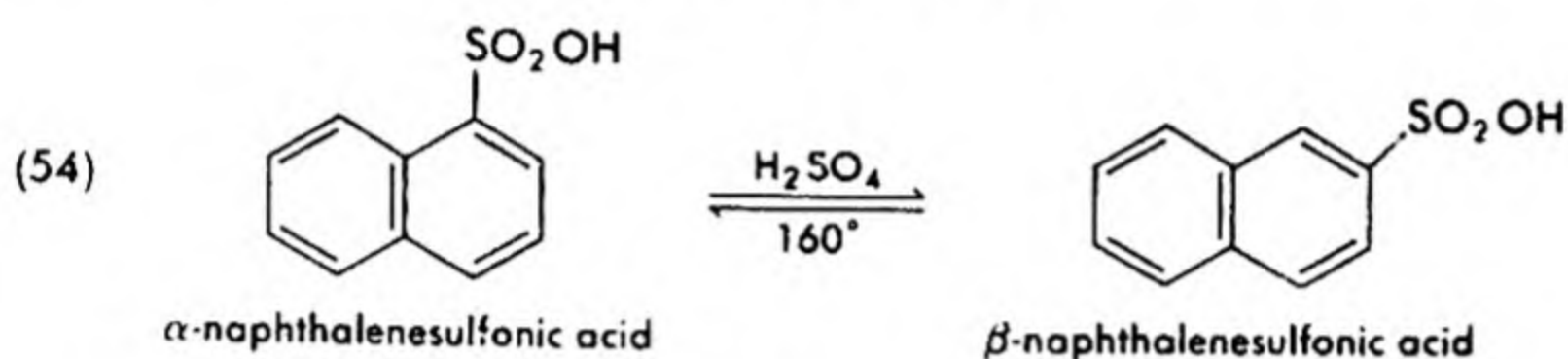
A. Migration of Substituents on Aromatic Rings

A number of examples of rearrangements of substituents on rings from one position to another have already been discussed. Among these are the Jacobsen rearrangement (see §16-6), where treatment of durene with

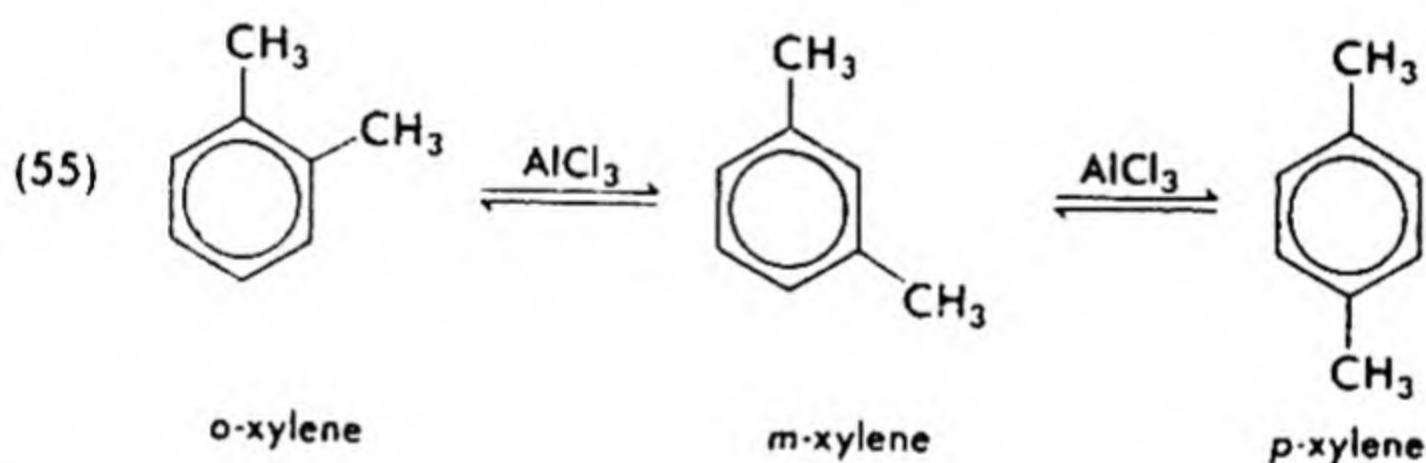
sulfuric acid leads to the formation not only of durenesulfonic acid but also of prehnitenesulfonic acid (eq. 53) and the rearrangement of α -naph-



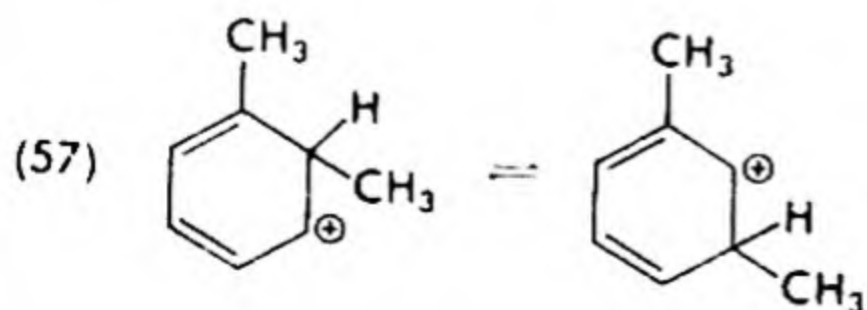
thalenesulfonic acid to the equilibrium mixture containing 85% of β -naphthalenesulfonic acid (eq. 54 and §16-5C.)

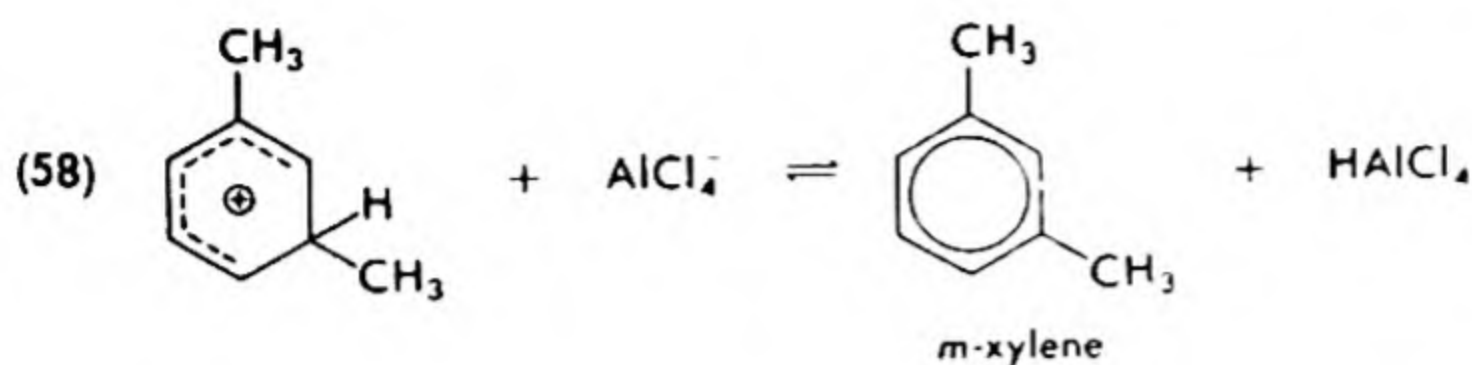


Such rearrangements are fairly general, another example being the isomerization of any of the xylenes to a mixture of all three under the influence of Lewis acids, particularly aluminum chloride (eq. 55).

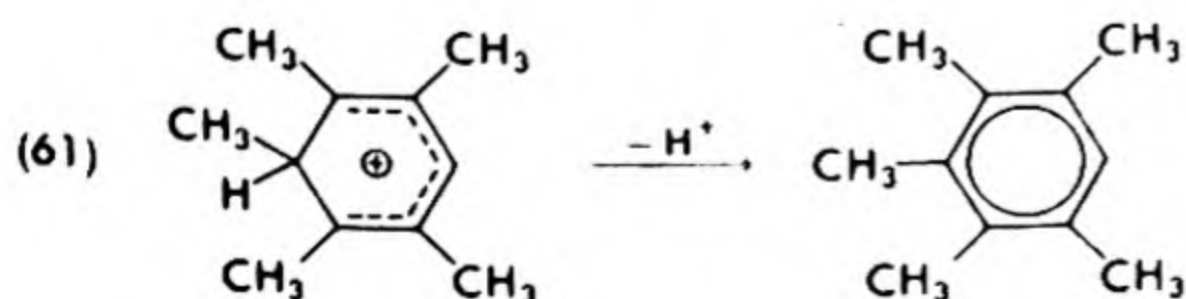
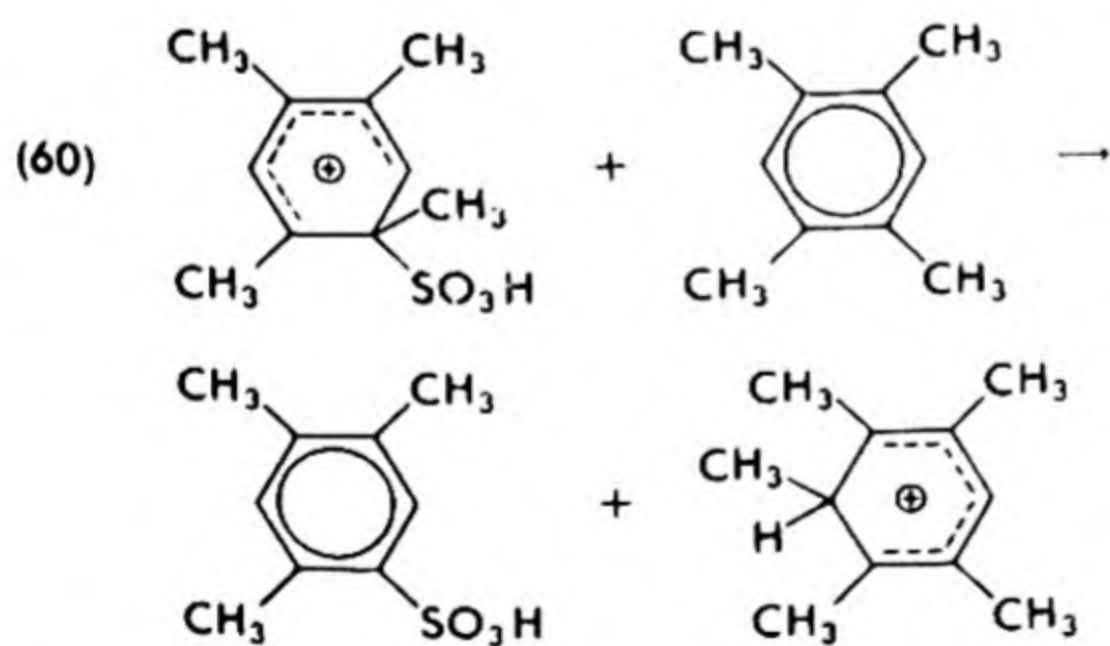
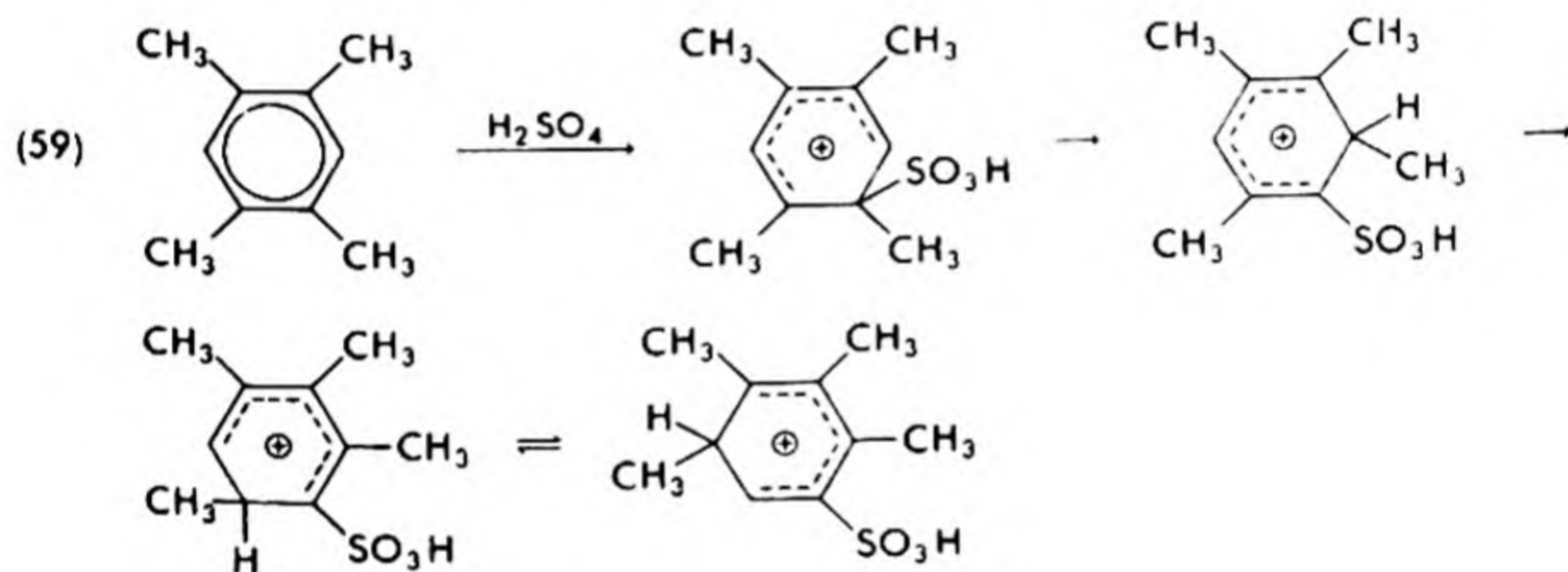


Several mechanisms are possible for such transformations. An intramolecular process for the latter reaction (eq. 55) may have the following steps (with one resonance structure indicated in eq. (57)).



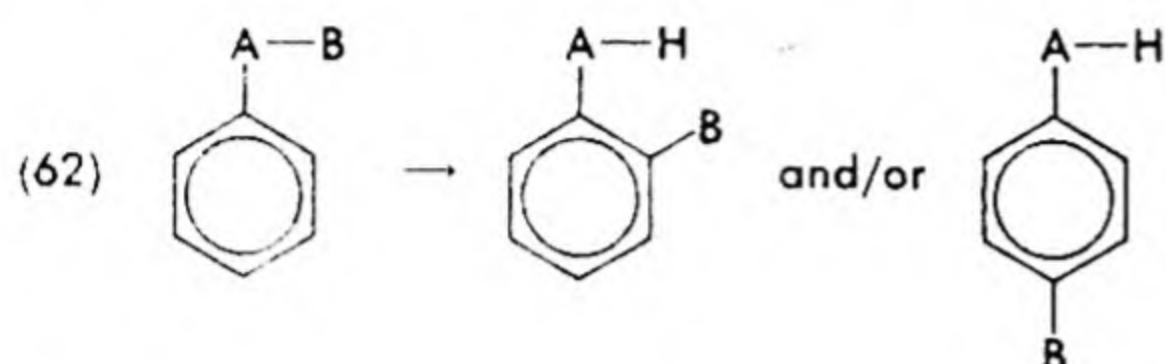


Intermolecular mechanisms are also involved, some of them representing the reversal of preparative processes, as in the desulfonation and resulfonation believed to occur in the reaction of eq. (54) and §16-5C. Others are required to rationalize the disproportionation accompanying the Jacobsen rearrangement. Here it is assumed that the reactions involved include that of eq. (59), describing rearrangement, and those in eqs. (60) and (61) giving the steps involved in the disproportionation reactions.

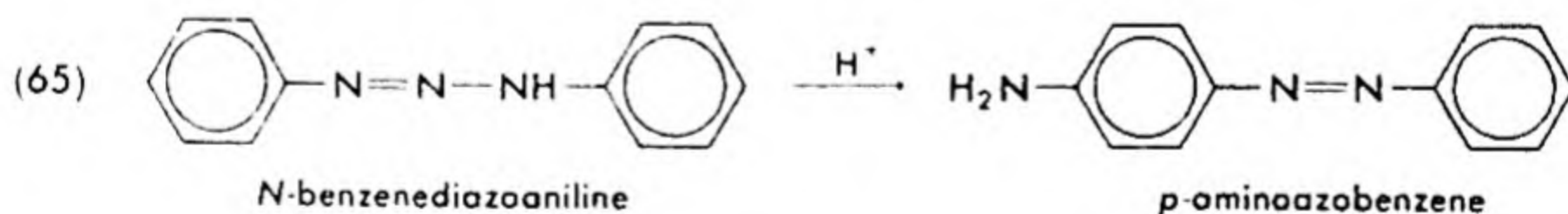
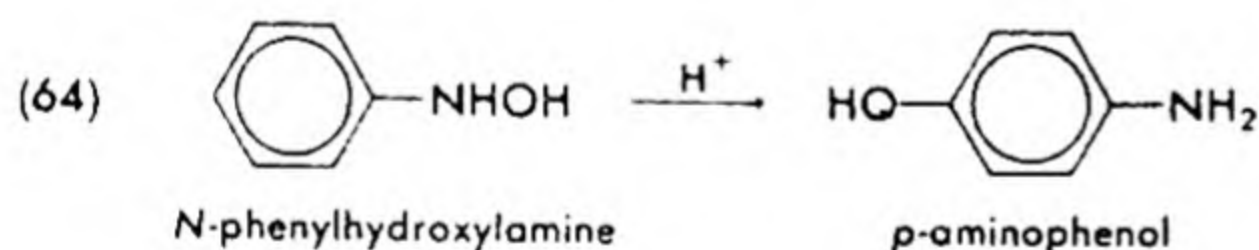
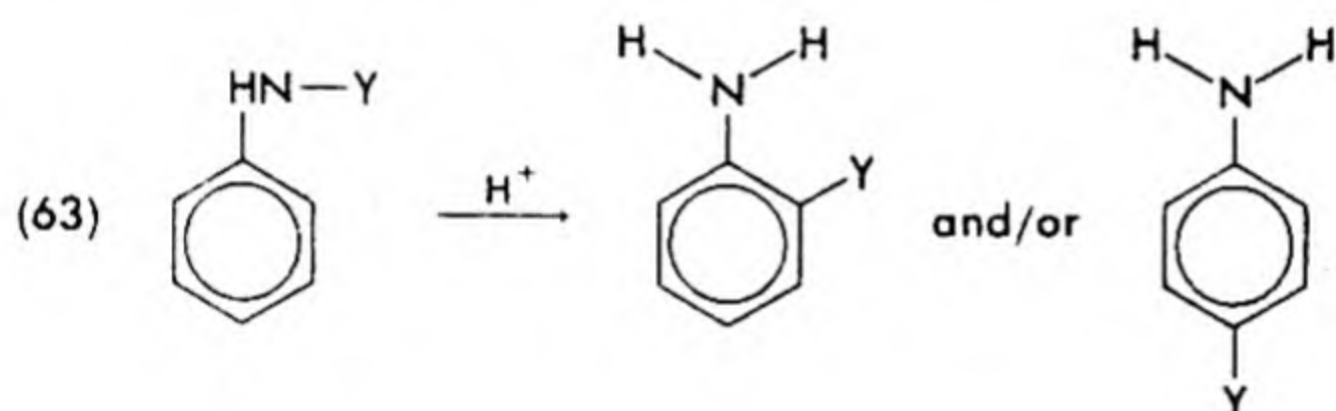


B. Rearrangements of *N*-Substituted Anilines and *O*-Substituted Phenols

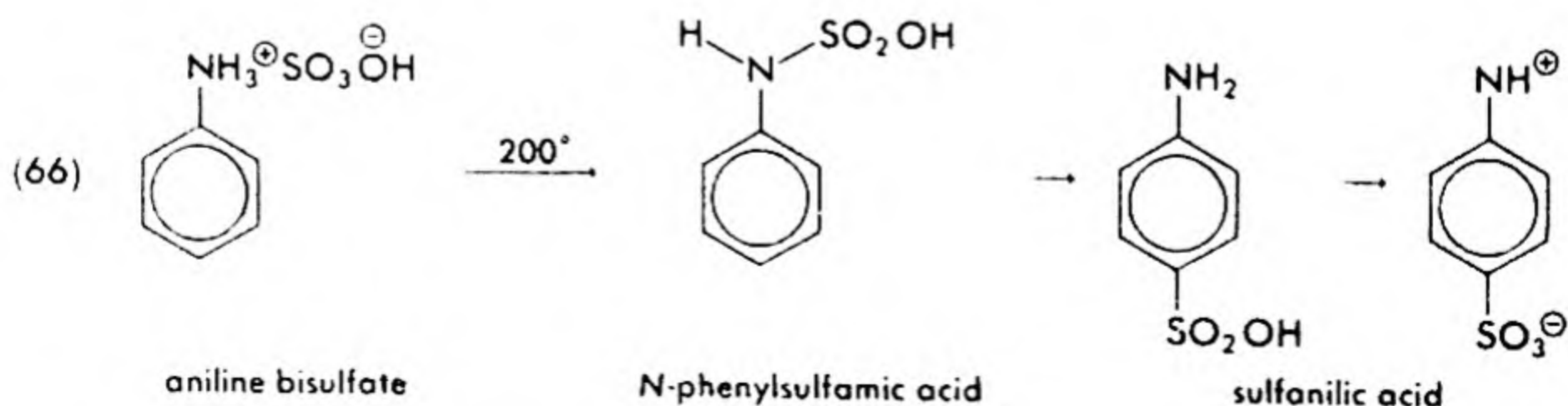
Perhaps a more important class of aromatic rearrangements is of the type represented in eq. (62), where A may be an oxygen or a nitrogen atom. These are generally, although not always, acid catalyzed.

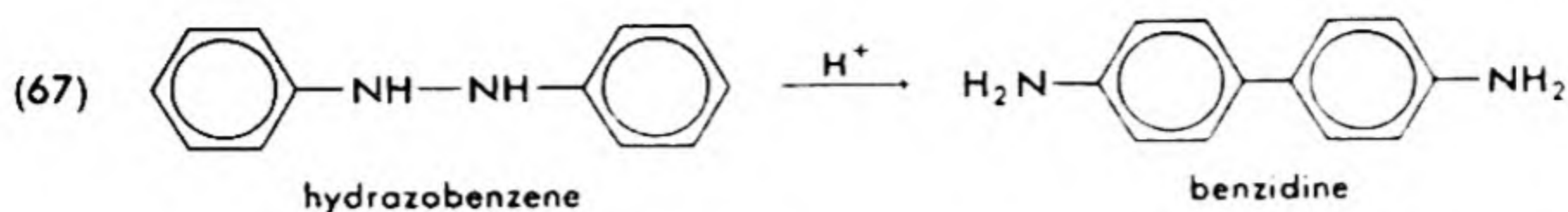


The general type of reaction discussed in this section is represented in eq. (63). Thus, treatment of *N*-phenylhydroxylamine with sulfuric acid yields *p*-aminophenol (eq. 64); *N*-benzenediazoaniline gives *p*-aminoazobenzene (eq. 65); baking the acid sulfate salt of aniline gives sulfanilic



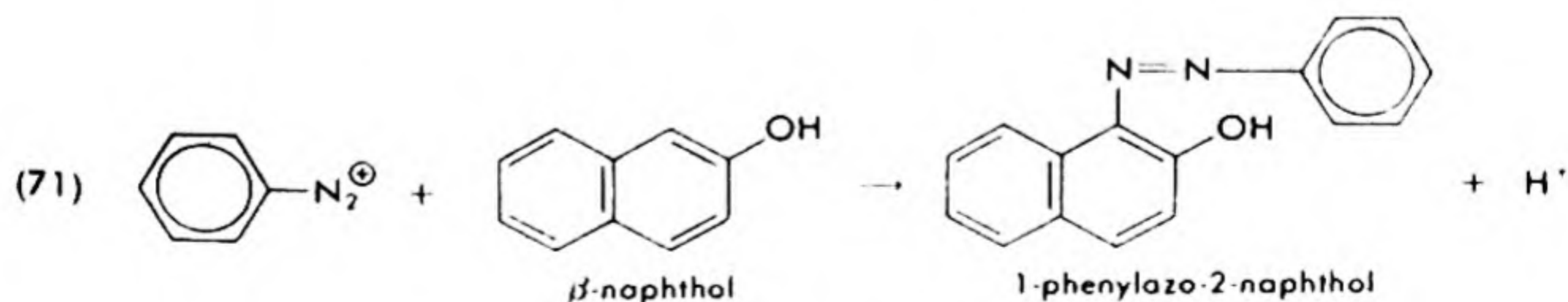
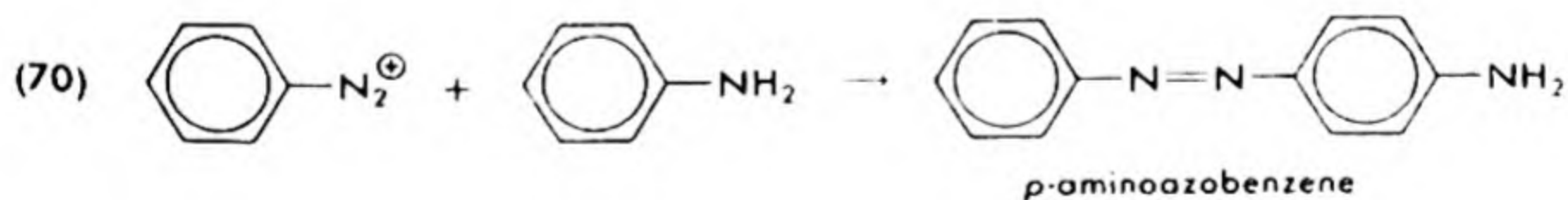
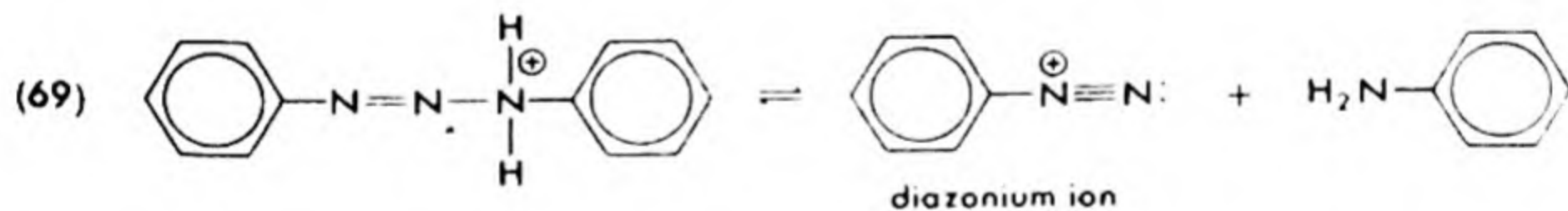
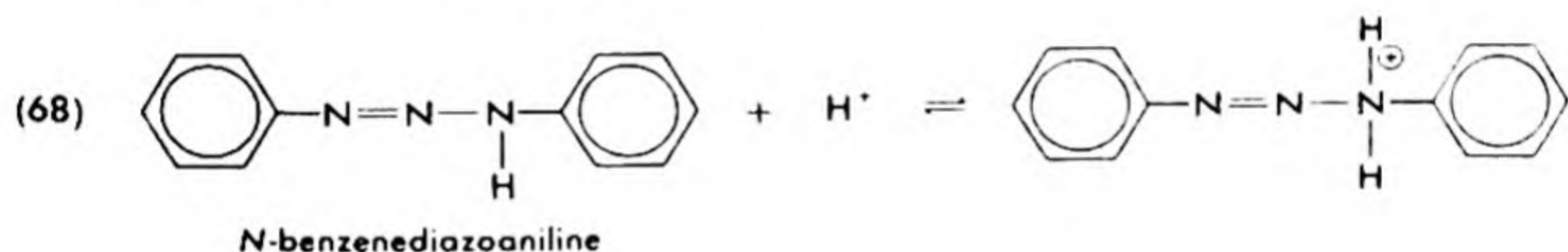
acid, presumably through *N*-phenylsulfamic acid (eq. 66), and hydrazobenzene is rearranged by acid to benzidine (eq. 67).





Many of these rearrangements are of considerable utility. The rearrangement in eq. (64) is undoubtedly involved in the electrolytic reduction of nitrobenzene to *p*-aminophenol in acid solution, and the *benzidine rearrangement* (eq. 67) is an important way of preparing diaminobiphenyls of considerable use in the dye industry. Although all the examples given above show nitrogen to *para* migration, some *ortho* product is generally observed. *Ortho* migration always occurs when the *para* position is already substituted.

Again both intramolecular and intermolecular mechanisms are involved. For example, the rearrangement of *N*-benzenediazoaniline (eq. 65) is clearly intermolecular (eqs. 68–71). The fact that the free diazonium ion is an intermediate in the reaction is demonstrated by the fact that it can be trapped by running the reaction in the presence of β -naphthol, whereupon reaction (71) occurs rather than (70).

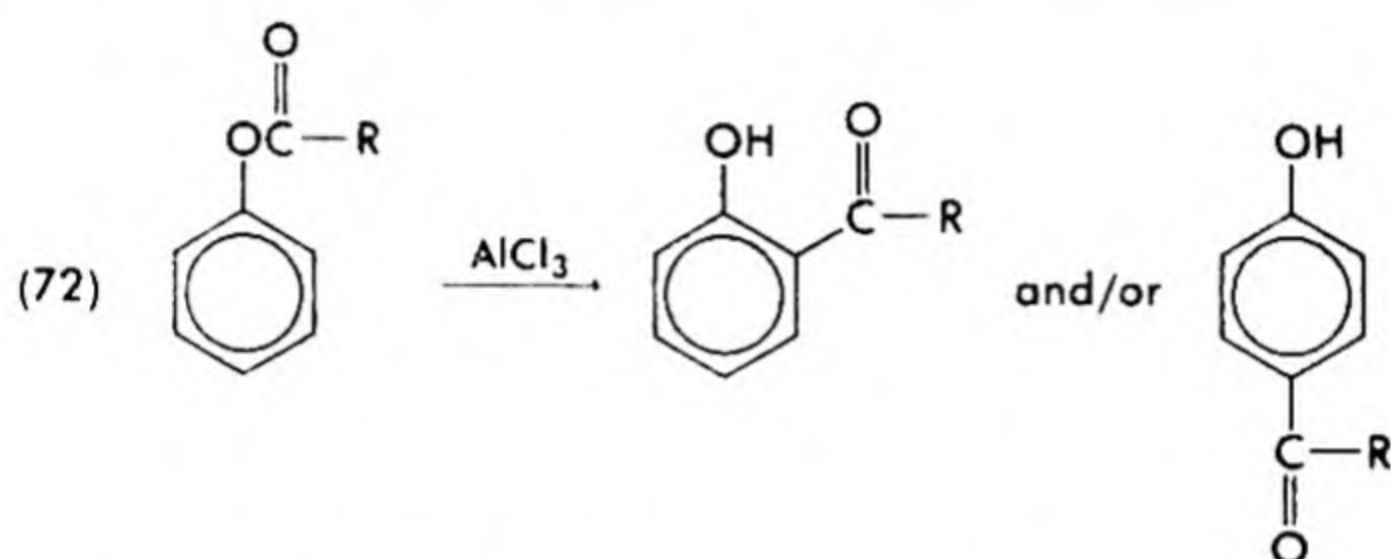


Although a great deal of work has been carried out on the benzidine rearrangement (eq. 67), the precise mechanism has not been agreed upon.

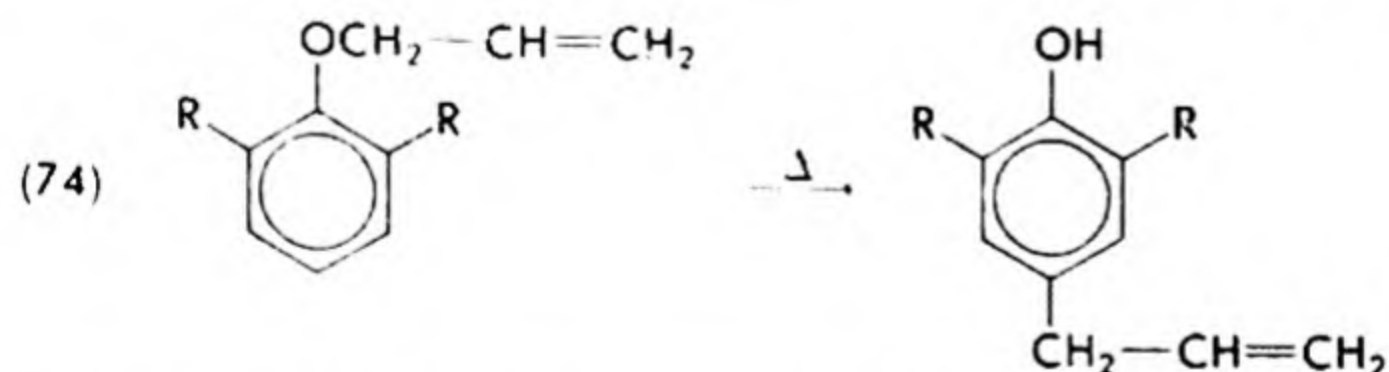
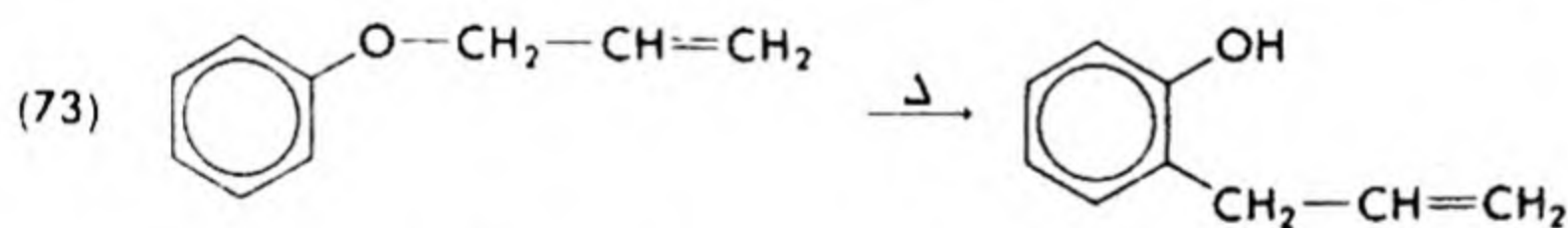
The mechanistic details must satisfy the facts that the reaction is acid catalyzed and intramolecular.

C. Migration of Substituents from Oxygen to Aromatic Rings

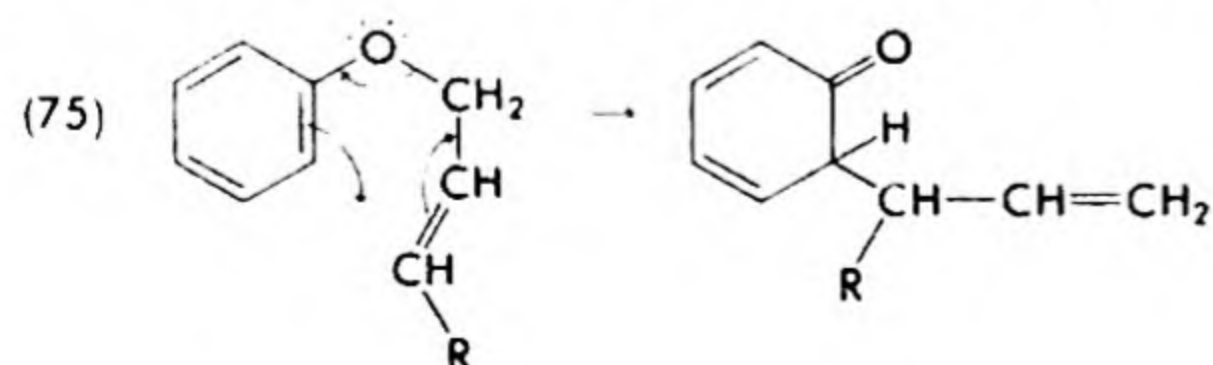
(1) *The Fries Rearrangement.* When the ester of a phenol is treated with aluminum chloride, it is converted to an *ortho*- or *para*-hydroxy ketone or to a mixture of them (outline 72). In general, the *para* product is favored at lower temperatures and the *ortho* at higher temperatures. The reaction is useful in synthesis, as phenols are not conveniently acylated by the Friedel-Crafts reaction.

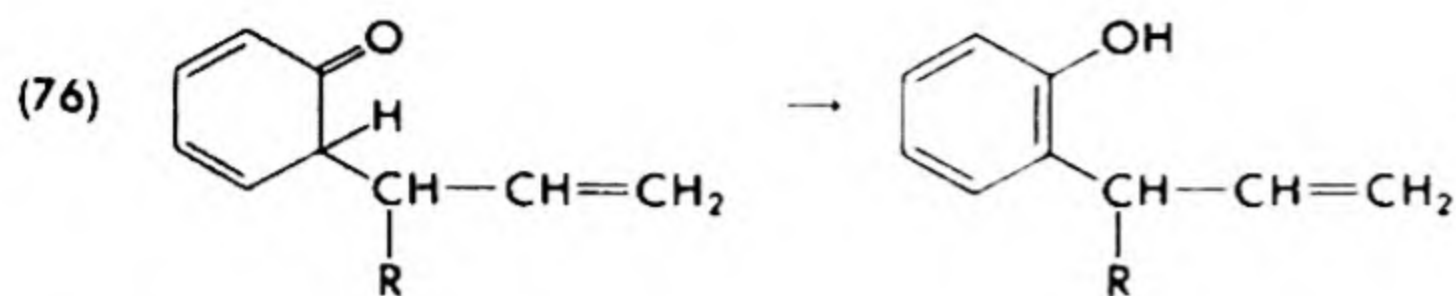


(2) *The Claisen Rearrangement.* When the allyl ether of a phenol is heated above 200°, it is smoothly rearranged to an allylphenol. So long as an *ortho* position is unsubstituted, the product is the *ortho*-allylphenol (eq. 73). When both *ortho* positions are blocked, *para*-migration occurs (eq. 74). Careful study has shown that the *ortho* rearrangement involves

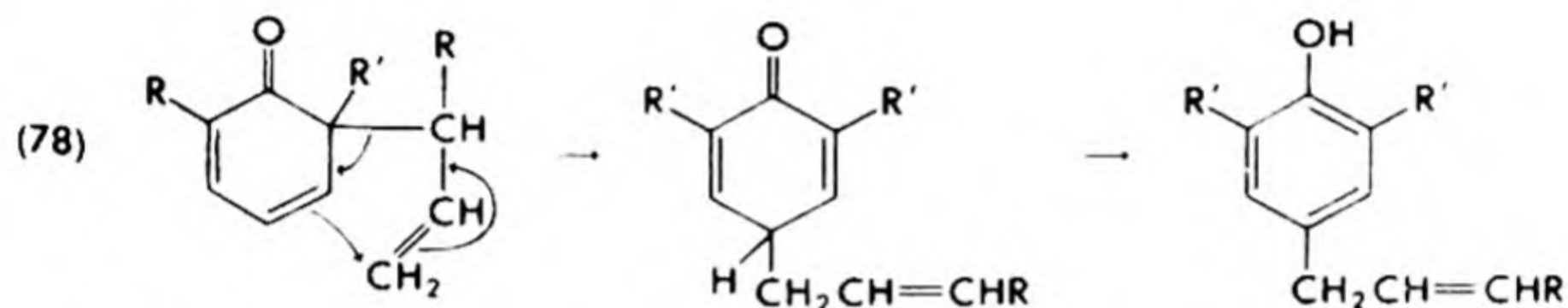
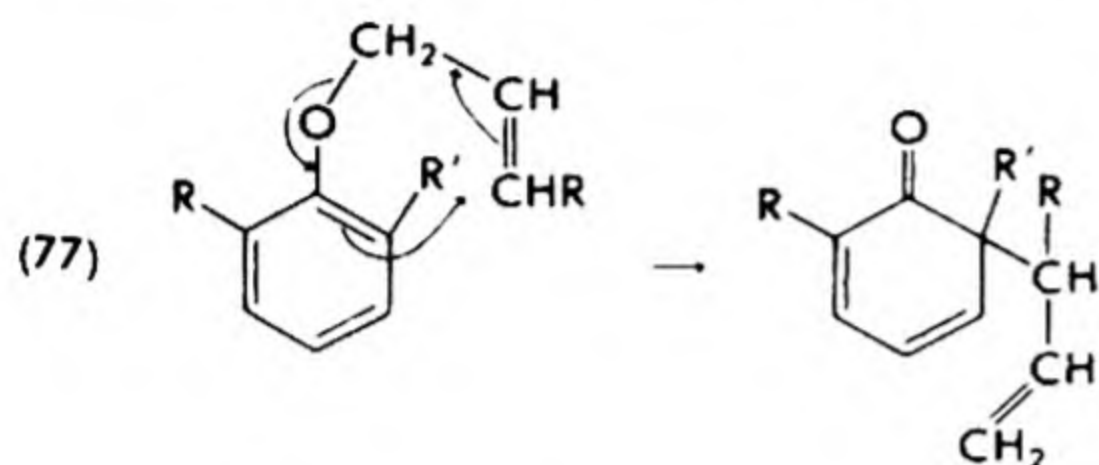


attack by the aromatic electrons at the remote end of the allylic system (eq. 75) giving a cyclohexadienone intermediate, which rapidly tautomerizes to the phenol. As indicated, the allylic group is clearly "inverted."

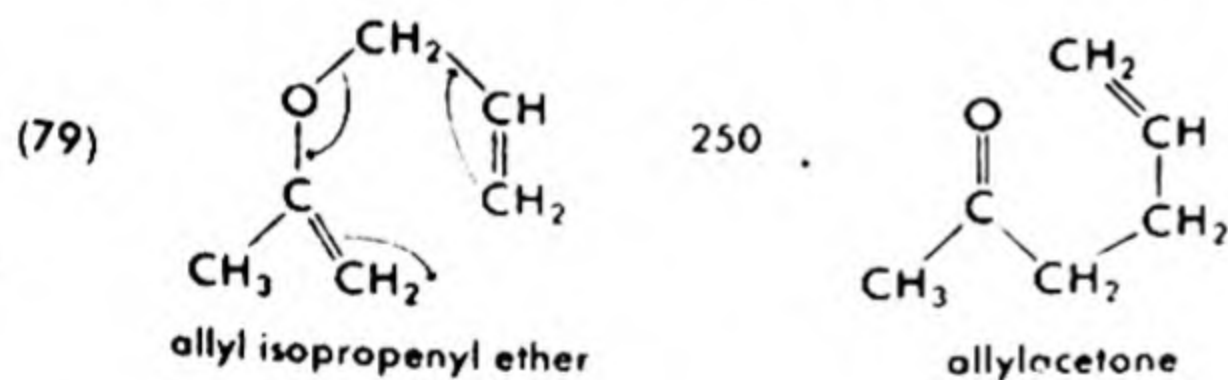




Migration to the *para* position occurs through two such dienone intermediates with net retention of allylic structure (eqs. 77-78).

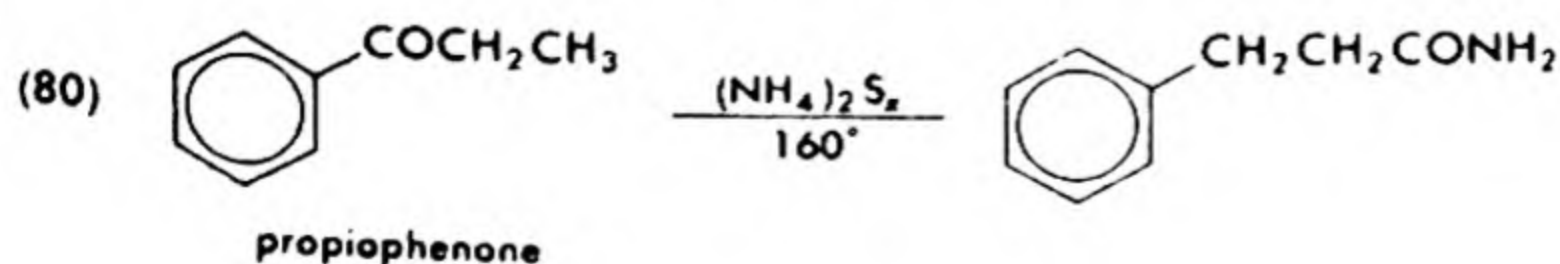


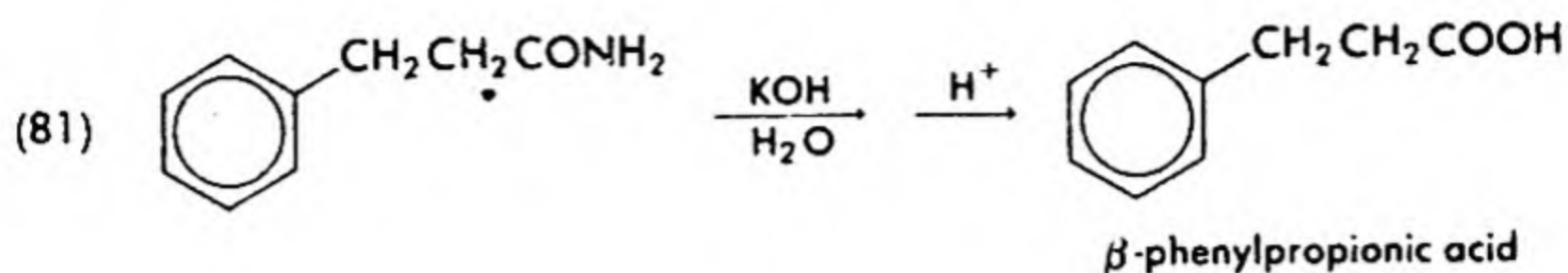
Similar thermal cyclic processes may occur in acyclic compounds. For example, heating allyl isopropenyl ether gives allylacetone in 85% yield.



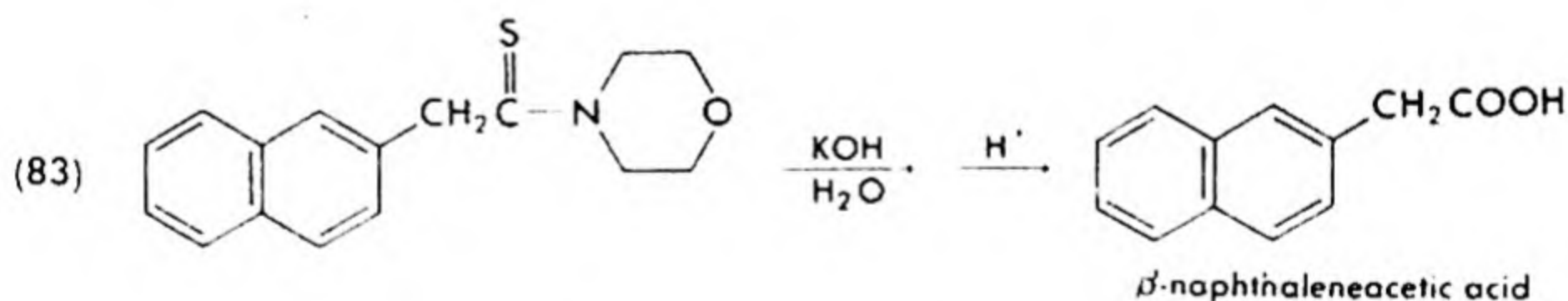
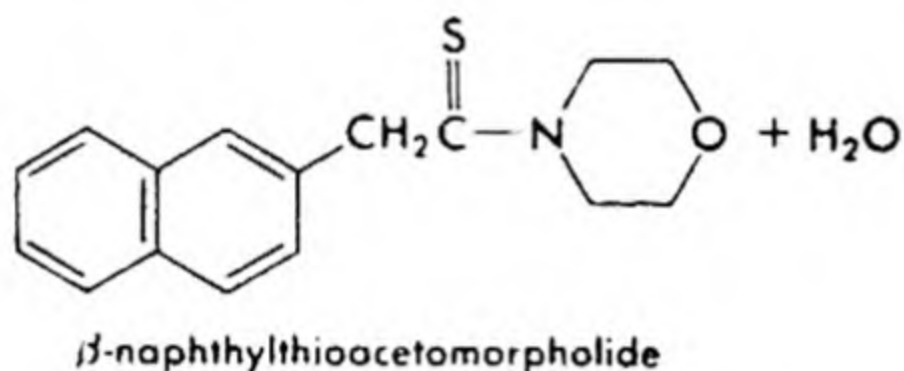
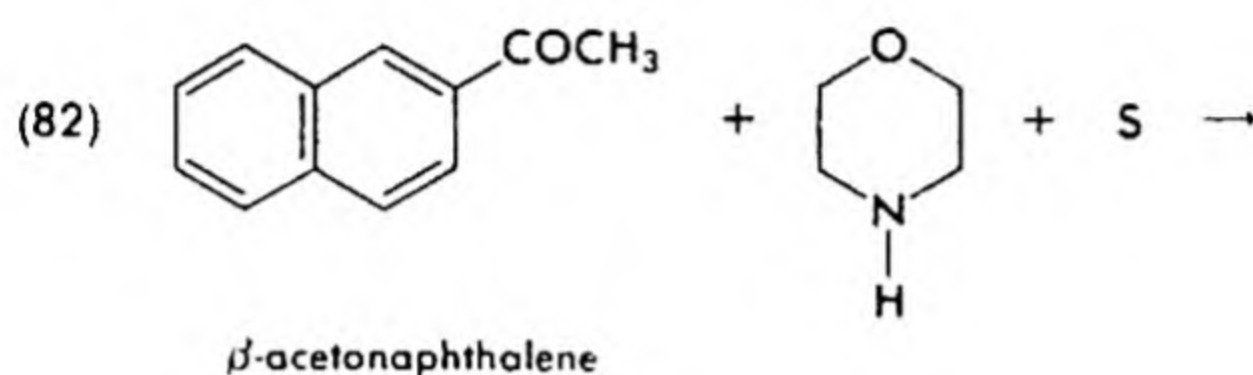
25-5 THE WILLGERODT REACTION

When an aryl alkyl ketone, ArCOR , is treated with a solution of ammonium polysulfide (sulfur dissolved in ammonium sulfide solution) in an autoclave, it is converted to an amide in which the functional group has migrated to the end of the chain. This is called the Willgerodt reaction and represents an effective way to prepare ω -arylalkanecarboxylic acids, since the ketones are readily available by the Friedel-Crafts reaction.





A modification of this reaction which avoids the use of a sealed tube or an autoclave uses morpholine and sulfur under anhydrous conditions. This gives the thiomorpholide product (eq. 82), which is readily hydrolyzed to the acid.



SUPPLEMENTARY READINGS

Gould, E. S., *Mechanisms and Structure in Organic Chemistry*, Holt-Dryden, New York, 1959.

Mayo, P. de, ed., *Molecular Rearrangements*, Interscience, New York, 1963, Part I.

QUESTIONS AND PROBLEMS

1. Write equations for reactions which occur when the following mixtures of compounds are treated under the proper conditions. Indicate the conditions. Use structural formulas for organic reagents and products.

- | | |
|---|--|
| a. 1,1,2,2-tetraphenylethane-1,2-diol and dilute hydrochloric acid | g. urea, sodium hypobromite, and sodium hydroxide |
| b. 1,1-diphenyl-2-methylpropane-1,2-diol and dilute hydrochloric acid | h. phthalimide, sodium hypobromite, and sodium hydroxide |
| c. 3,3-diethyl-2-pentanol heated with concentrated sulfuric acid | i. <i>syn-n</i> -butyraldoxime and polyphosphoric acid |
| d. 3-phenyl-1,2-naphthaquinone and sodium hydroxide | j. <i>anti-n</i> -butyraldoxime and polyphosphoric acid |
| e. benzoyl chloride and sodium azide | k. 3,3'-dinitrohydrazobenzene and hydrochloric acid |
| f. octanoyl azide heated | l. α -binaphthoyl and sodium hydroxide |

2. Show how the following syntheses can be performed as advantageously as possible from the indicated starting materials and inorganic reagents. Use structural formulas for organic compounds. Indicate reagents and necessary special conditions.

- | | |
|---|--|
| a. phenyl isocyanate from benzoic acid | e. 3,3'-dihydroxy-4,4'-biphenylenediamine from phenol |
| b. <i>p</i> -hydroxybenzophenone from phenol and benzoyl chloride | f. 2-(1-phenylallyl)phenol from benzene and acetic acid |
| c. <i>o</i> -phenylenediamine from phthalic acid | g. 4-phenyl-3-butenamide from benzaldehyde, acetic anhydride, and diazomethane |
| d. <i>n</i> -butylamine from valeric acid | |

26

Free Radical Reactions

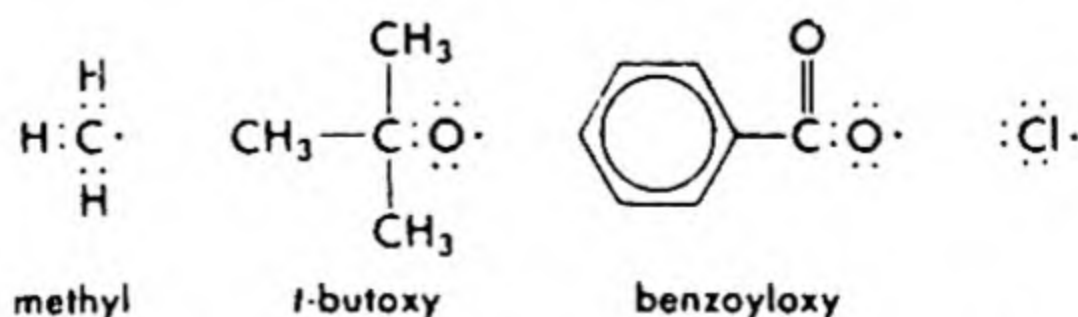
26-1 NATURE OF FREE RADICALS

During the early development of chemistry, the term *radical* was used to denote a group which maintained its integrity during the course of a reaction. Thus, for example, the ethyl "radical" retained its identity in the transformation of ethyl alcohol to ethyl bromide.

Wurtz believed that his treatment of ethyl bromide with sodium gave free ethyl radicals, but subsequent molecular-weight determinations showed that in fact dimeric products resulted from the *Wurtz reaction* (eq. 1).



Experiences such as these led organic chemists to believe that, with few exceptions (e.g., carbon monoxide, isonitriles), only tetravalent carbon compounds could be isolated. In 1900, however, Moses Gomberg demonstrated the existence of the first stable organic free radical, and since that time much evidence has accumulated for the intermediacy of free radicals in both organic and inorganic reactions. As discussed earlier (§11-2A and §15-1), *radicals* or *free radicals* (terms now generally used interchangeably) are species (neutral or charged) with one or more *unpaired electrons*. The odd electron may be associated with a carbon atom as in methyl, an oxygen atom as in *t*-butoxy or benzoyloxy, a halogen such as a chlorine atom, and so on. We shall ordinarily denote a free radical by using a dot to represent the unpaired electron, $\text{Y}_3\text{C}\cdot$ for example.



A carbon free radical may be planar (Fig. 26-1A) with the unpaired electron in a *p* orbital, although this is not certain. If the radical is tetra-

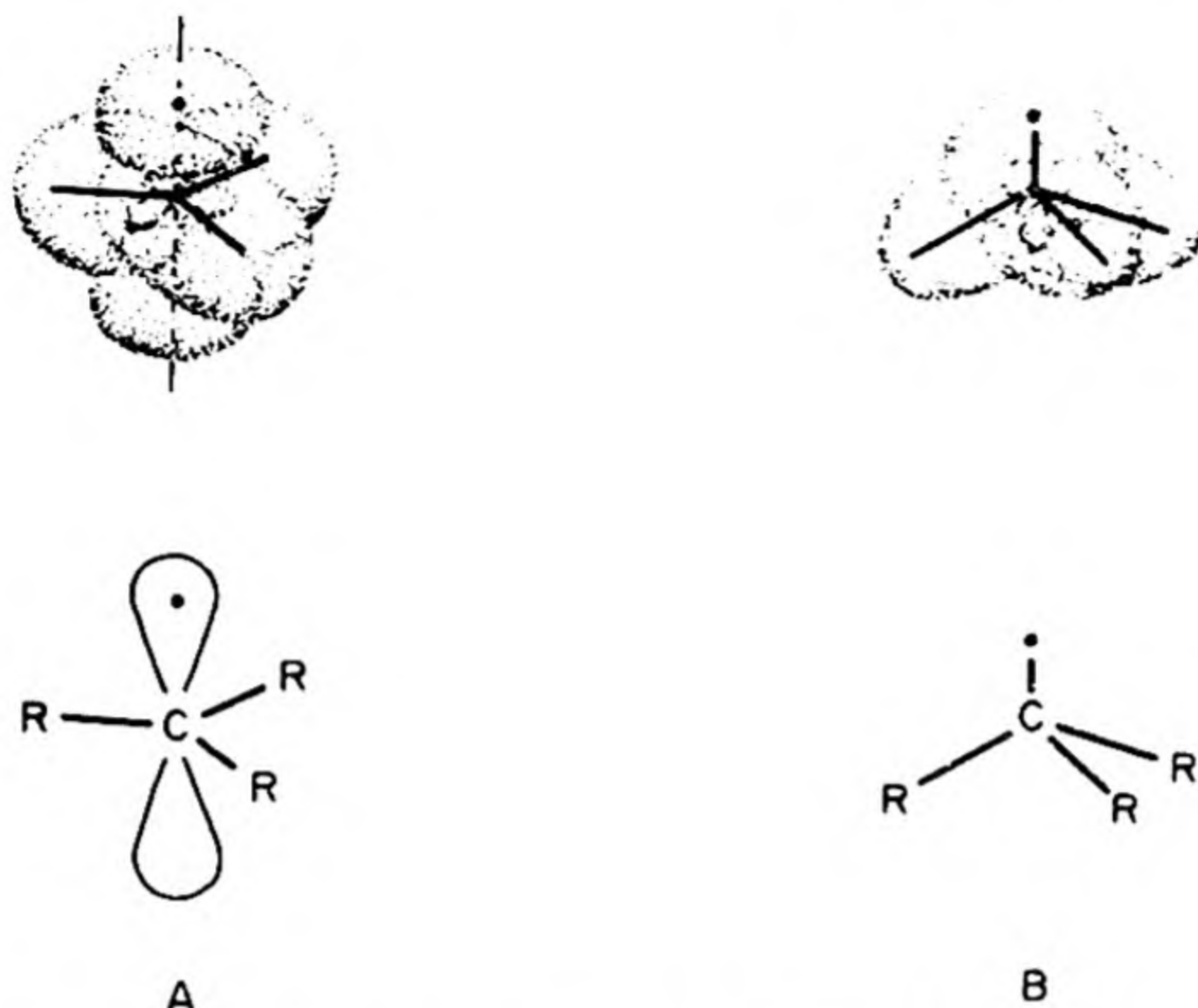


Fig. 26-1. Alternative Representations of an Organic Free Radical. (A) Planar model, (B) Pyramidal model.

hedral (Fig. 26-1B), it almost certainly oscillates rapidly with inversion of configuration.

26-2 EVIDENCE FOR FREE RADICALS

It is now clear that many organic reactions involve free radical intermediates. Before considering details of individual mechanisms, it is worthwhile to consider some of the evidence for the existence of these ordinarily short-lived species.

In 1929-31 Fritz Paneth and his students at the University of Berlin were successful in demonstrating the existence of free methyl and free ethyl radicals. The apparatus used is shown in Fig. 26-2. Paneth placed in

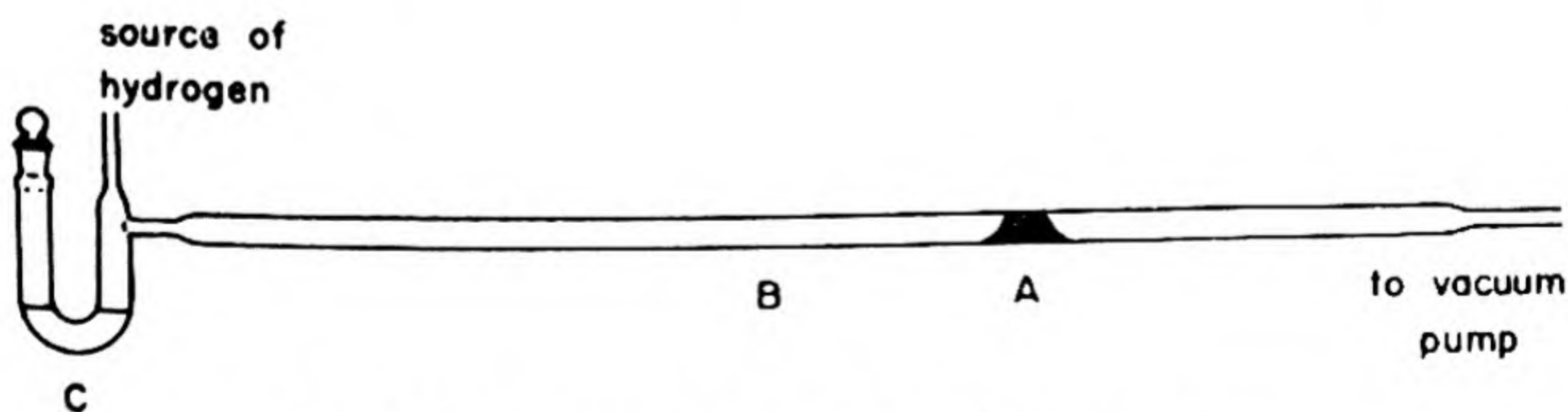
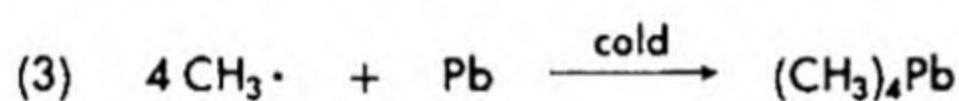
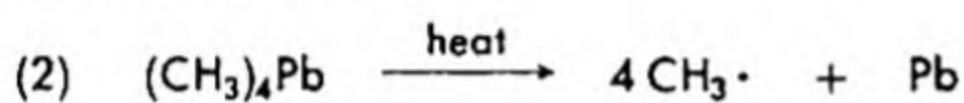


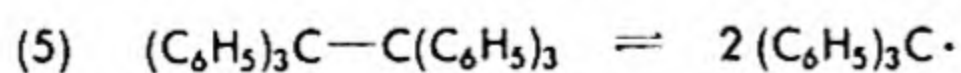
Fig. 26-2. Apparatus for the Paneth Experiment.

the tube, C, a sample of tetramethyllead or tetraethyllead, which was evaporated into a stream of hydrogen down an evacuated tube. Heating the tube strongly at one point, A, decomposed the tetraalkyllead and deposited a lead mirror at that point. When tetramethyllead was used, ethane was found in the gas pumped out of the tube. When the flame was moved back to another point, B, on the upstream side of the original mirror, a new lead mirror was formed and the old one disappeared. Tetramethyllead was found this time in the effluent gas. If the distance between A and B was too large, the first mirror did not disappear, but only ethane was found in the effluent gas mixture. The only plausible explanation was that methyl radicals had separated from the lead atoms at the point of heating. When there was a lead mirror close enough for them to react with it before they had all combined with each other, they reacted with this to form tetramethyllead. When there was no mirror, or the mirror was too far along, the free methyl radicals combined with each other to form ethane.

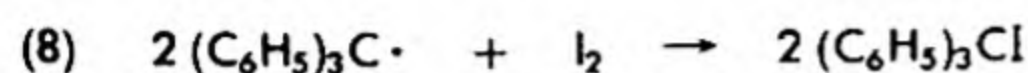
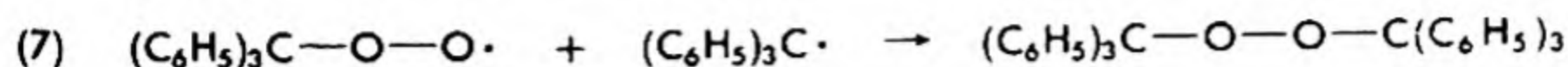
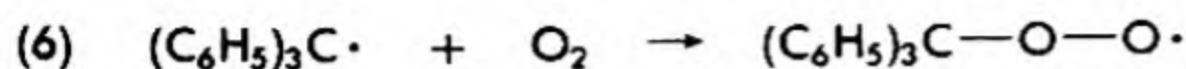


Similar results were obtained in the experiments with tetraethyllead. By simple measurements Paneth estimated the half life, or time it takes for half of the methyl radicals to disappear, to be 0.006 sec. at a pressure of 2 mm. in hydrogen. Measurements on other alkyl free radicals have shown that they have half lives of the same order of magnitude.

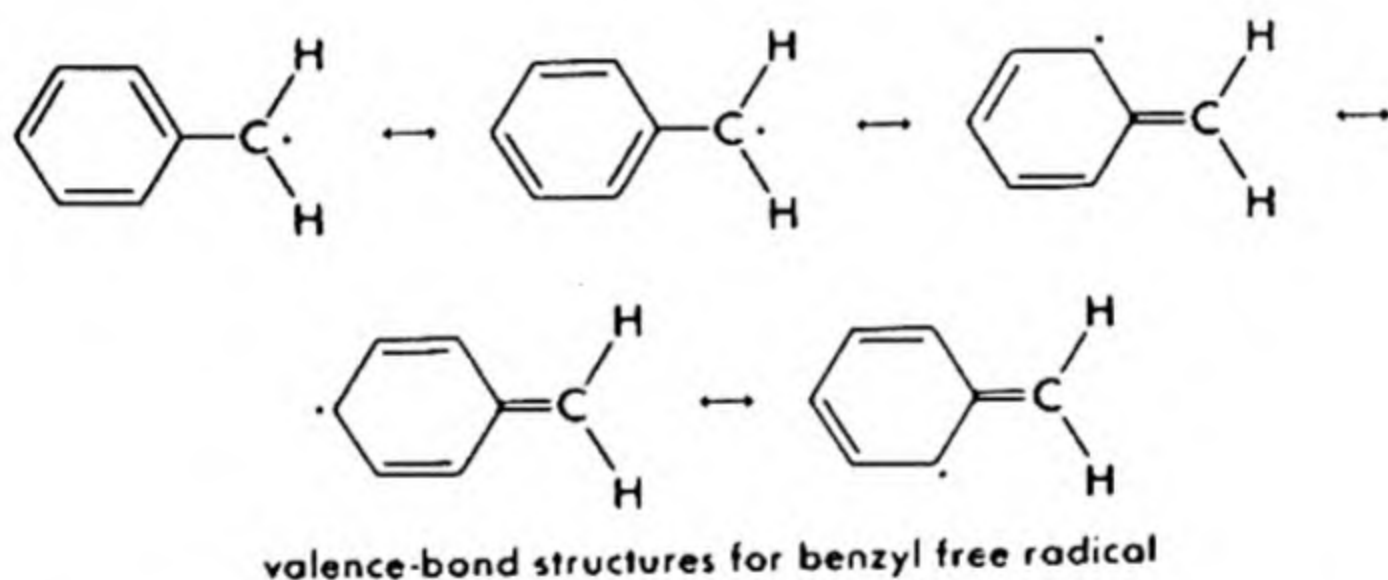
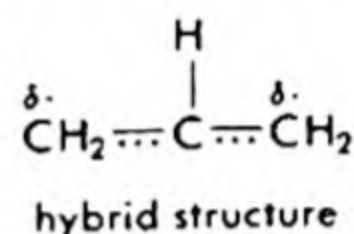
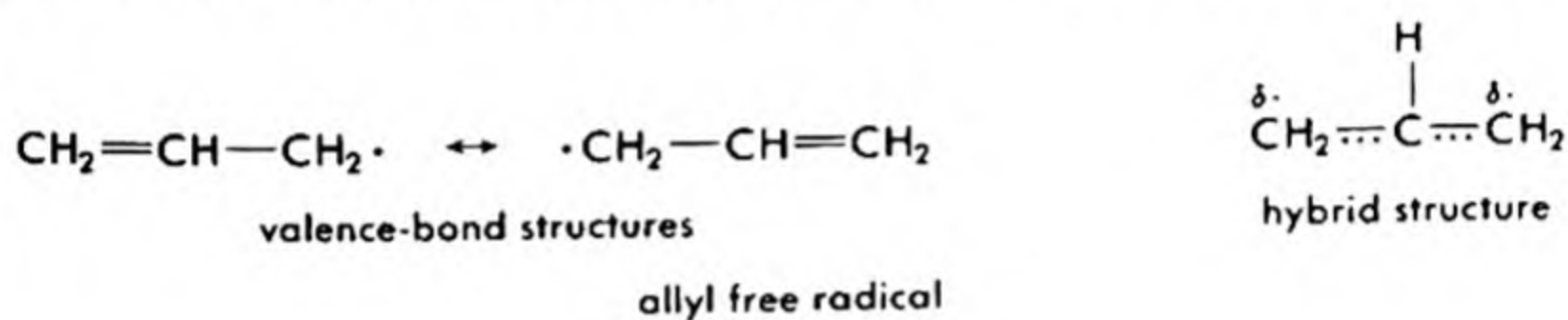
Well before the Paneth experiment, Moses Gomberg had shown that certain types of free radicals are stable enough to be isolated. In 1900 Gomberg prepared hexaphenylethane (a white solid) by treatment of triphenylchloromethane with silver. This substance gave a yellow solution which reacted rapidly with atmospheric oxygen and iodine, reactions that have since been shown to be characteristic of free radicals. The solution was nonconducting, so that ions could not be responsible for the color. Heating the solution increased the depth of the color and reactivity of the mixture; cooling it decreased both. It was apparent that an equilibrium was involved in which hexaphenylethane decomposed to form triphenylmethyl free radicals (eq. 5).



The triphenylmethyl radicals react with oxygen to give triphenylmethyl peroxide (eqs. 6 and 7) or with iodine to give triphenylmethyl iodide (eq. 8).

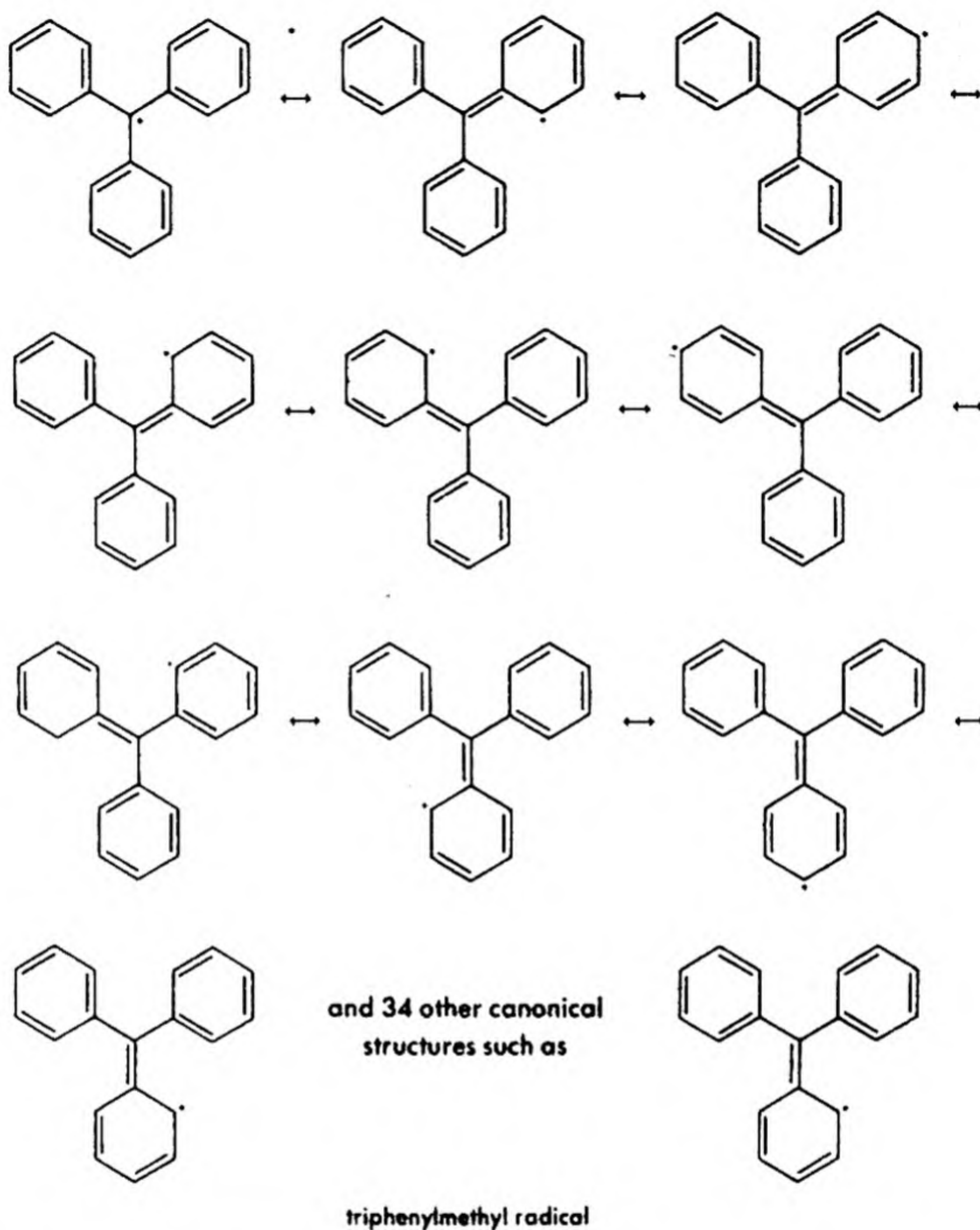


It is quite clear from the discussion above that triphenylmethyl is a much more stable radical than is methyl radical, and it is a fact that stability increases in the order methyl, benzyl, benzohydryl (diphenylmethyl) to triphenylmethyl. Similarly, the allyl radical is more stable than methyl. A large share of the stabilization of these radicals is due to resonance, analogous to that described for carbonium ions (§12-1B(4)). For example, the odd electron in allyl is delocalized over the three-carbon π system, as indicated below. Electron delocalization in the benzyl radical distributes the odd electron over the *ortho* and *para* positions. The odd electron in

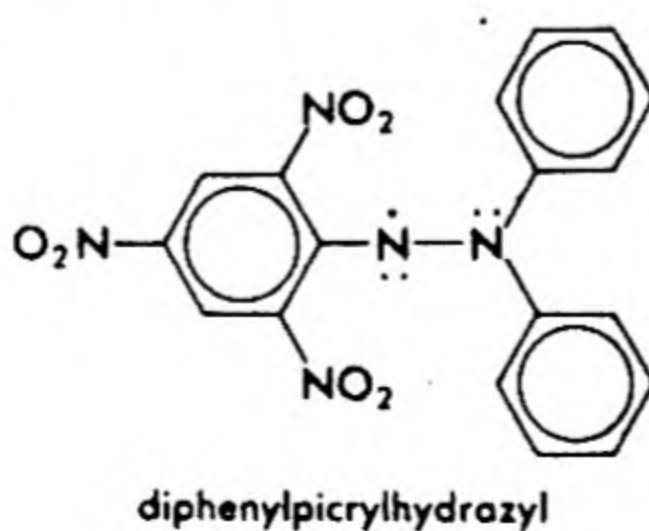


triphenylmethyl is delocalized throughout the three rings, so that this radical is greatly stabilized compared with an ordinary alkyl radical (see below and Fig. 12-11). In the dimer hexaphenylethane the electrons are paired in a *localized* covalent bond. The delocalization energy gained in the separation into radicals compensates in part for the loss of covalent bond energy and is therefore at least partly responsible for the dissociation into triphenylmethyl radicals. Steric relief is the second factor in the instability of hexaphenylethane. The six phenyl groups are very crowded. Formation of triphenylmethyl radicals relieves much of this crowdedness.

Free radicals can be detected by means of the following properties: paramagnetism, or attraction to a magnet by response to its magnetic field; absorption of oxygen or of nitric oxide; rapid decolorization of iodine; rapid decolorization of diphenylpicrylhydrazyl, a violet-colored



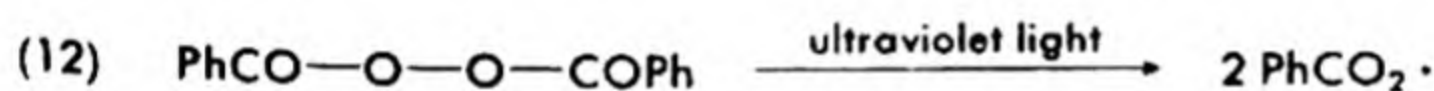
stable free radical; sometimes formation of transient colors or colored solutions which change in intensity of color with change in temperature. Recently, much information has been made available regarding the structure of free radicals by electron paramagnetic resonance (§34-4).



26-3 FORMATION OF FREE RADICALS AND INITIATION OF FREE RADICAL PROCESSES

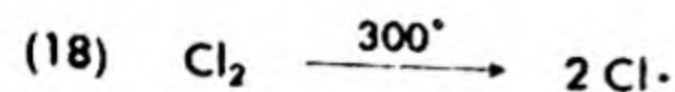
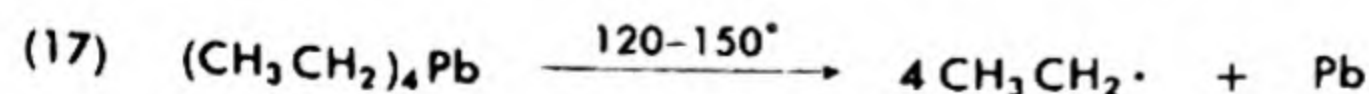
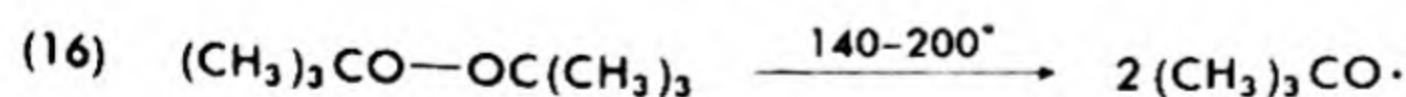
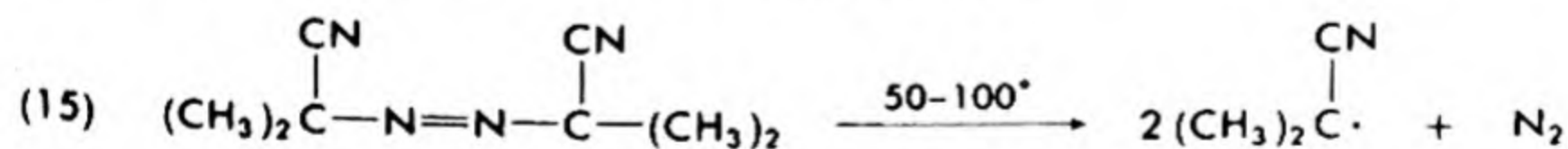
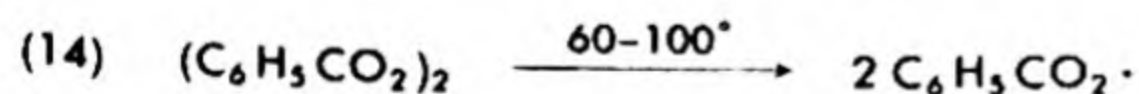
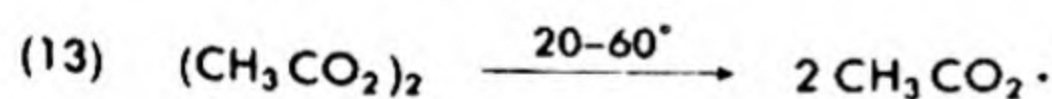
Normally, free radicals are unstable with respect to the molecules to which they are related; that is, methyl is unstable with respect to ethane, chlorine atoms with respect to chlorine molecules, and so forth. It is therefore necessary to add sufficient energy to a molecule to disrupt one of its covalent bonds (usually the weakest one). Such a reaction is called *homolysis* (§11-2A) and results in the formation of free radicals in pairs.

There are two principal methods for adding energy to a molecule. One is heating the molecule; the other is subjecting it to radiation which it can absorb. The radiation may be ultraviolet light, visible light (if the substance is colored, see §33-2D), x-rays, or γ -rays. Photochemical dissociation is generally preferred over that with higher energy radiation as more selective reactions ordinarily result. Some examples of the formation of radicals by irradiation are given in eqs. (9) to (12).



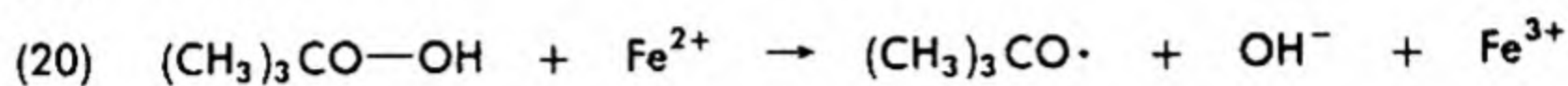
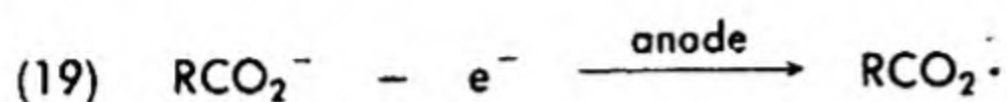
In such reactions, a quantum of light ($h\nu$) is absorbed by the molecule, and the energy of that quantum is utilized to disrupt the bond.

The temperatures required for thermal activation depend on the stability of the bond to be broken. Some temperatures for useful decomposition rates are as follows:



Radicals can also be produced by single-electron oxidation-reduction, either by electrolysis or with chemicals. By anodic oxidation (eq. 19),

acyloxy radicals result from salts of carboxylic acids. An example of the formation of a radical by a chemical reduction is given in eq. (20).

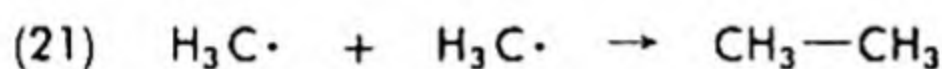


26-4 FREE RADICAL REACTIONS

Free radicals undergo several types of reactions, some of which resemble heterolytic reactions (hence they often confused early organic chemists by the discrepancies in the nature of products formed in and the rates of certain reactions). A few of these have already been considered in Chapter 15.

The main reaction types are the following:

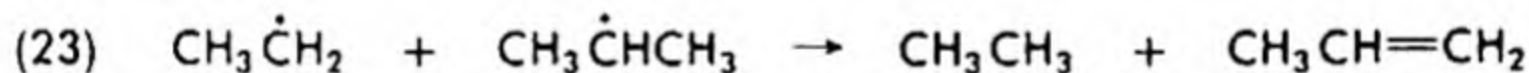
Coupling:



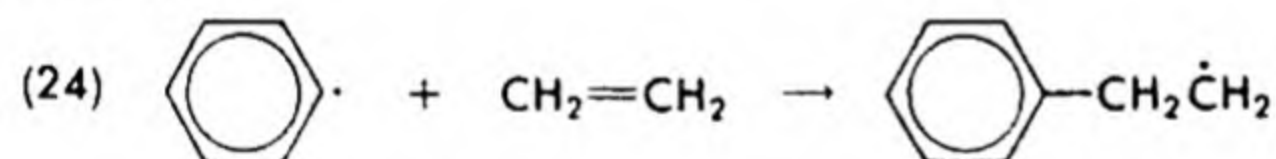
Displacement:



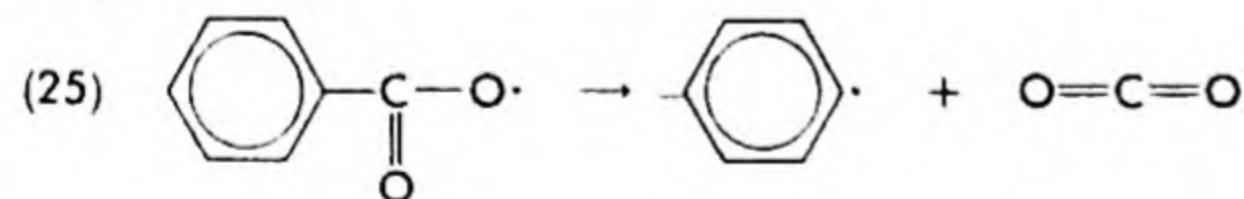
Disproportionation:



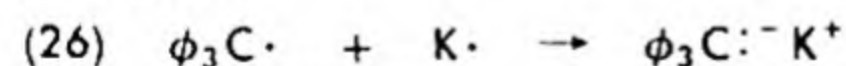
Addition:



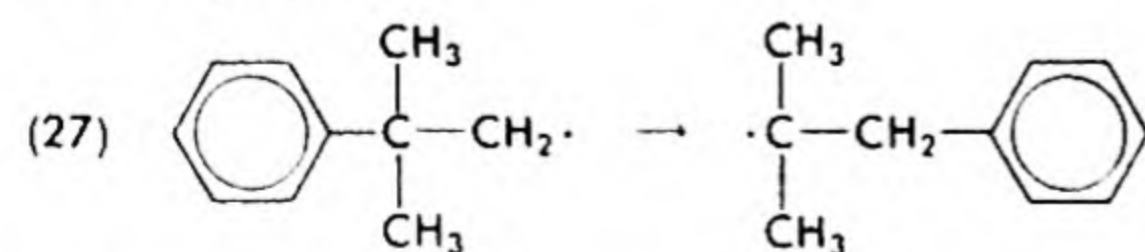
Fragmentation:



Reduction:



Rearrangement:



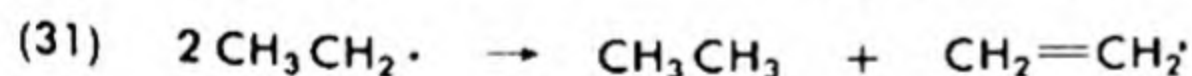
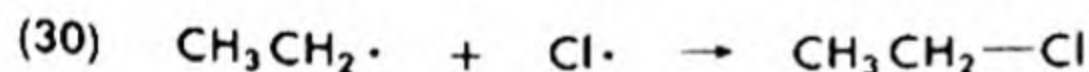
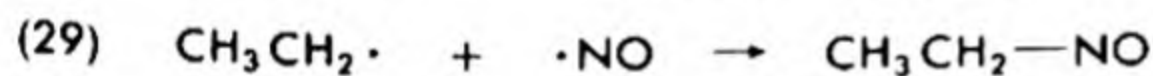
Several of these reactions may be involved as steps in one stoichiometric "reaction." Some of the various combinations which can occur are shown in the subsequent sections.

Other names are used for some of these reactions in certain contexts. Thus, coupling, (eq. 21), and disproportionation, (eq. 23), are often *termination*, since these processes stop a free radical process by destroying radicals. Displacement, (eq. 22), is also *chain transfer*, the transfer of radical activity from one particle to another.

Sequences of radical reactions are often *chain reactions* (§15-1A), processes in which a new active radical is formed in each step, so that the presence of a reactive intermediate is maintained for many steps until a chain termination intervenes. Steps which can participate in chain reactions are displacement, (eq. 22), addition, (eq. 24), fragmentation, (eq. 25), and rearrangement, (eq. 27). In each such step, one odd-electron reagent species is involved, so that there must always be an odd electron on one of the product species.

A. Radical Combination Reactions; Termination Processes in Radical Reactions

While radicals have many reactions in which the number of unpaired electrons remains constant, some of which are described in following sections of this chapter, ultimately two radicals may combine to form one molecule (or more) in which the electrons are paired. Such reactions are called radical-combination or termination processes. The two radicals may be alike or they may be different, and terminations may occur by combination, eqs. (28) to (30) or by disproportionation (eq. 31).

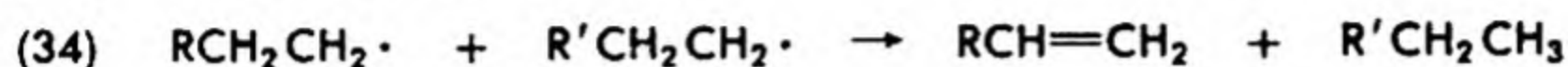
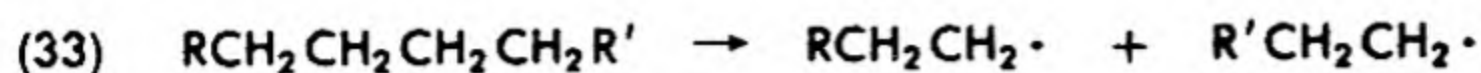


Two atoms cannot dimerize by themselves, as they have no internal possibilities of getting rid of the energy that must be evolved to form a stable bond. (More complicated systems can dispose of excess energy in thermal vibrational and rotational excitation, see §33-3.) Free atoms, therefore, need a third body (wall, other molecule, etc.) to which the excess energy can be liberated as heat (eq. 32).



B. Thermal Reactions of Paraffins

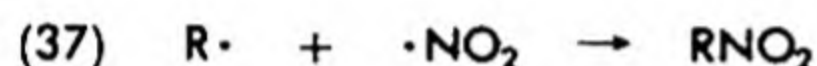
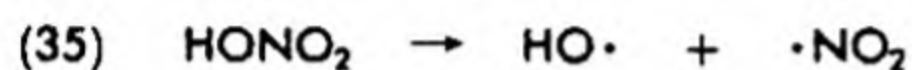
The uncatalyzed pyrolysis of petroleum fractions to give gasoline and gas fragments (§44-1C(1)) undoubtedly involves free radical intermediates. A long-chain hydrocarbon may cleave at any one of its bonds to give two radicals, which can then disproportionate to paraffin and olefin (eqs. 33 and 34) or undergo depolymerization (§26-6, eq. 59).



C. Free Radical Substitution

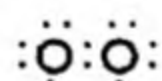
Substitution reactions in alkanes and, under appropriate conditions, in many other compounds occur through free radical chain processes. Halogenation has already been discussed (§15-2 and §15-3). Other substitution reactions of interest are nitration and hydroperoxide formation.

(1) *Nitration.* When nitric acid is present at high temperatures, it decomposes to hydroxy radicals, which may initiate chains, and nitro radicals, which react with alkyl radicals to give nitroalkanes (eqs. 35 to 37). This is the basis of the commercial formation of nitroalkanes.



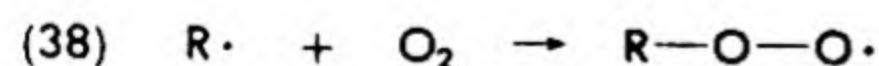
The nitration reaction is much more complex than halogenation, since fragmentation and oxidation reactions compete with substitution. However, there is evidence to show that selective attack on hydrogen atoms at branched positions occurs; in the nitration of propane at 420°, nearly equal amounts of 1-nitropropane and 2-nitropropane are obtained, along with nitroethane, nitromethane, and oxidation products.

(2) *Hydroperoxide Formation; Autoxidation Reactions.* Evidence from many sources makes it clear that oxygen molecules do not contain doubly bonded oxygen atoms, but instead that oxygen is a diradical in which one unpaired electron exists in a *p* orbital on each oxygen atom. One result of



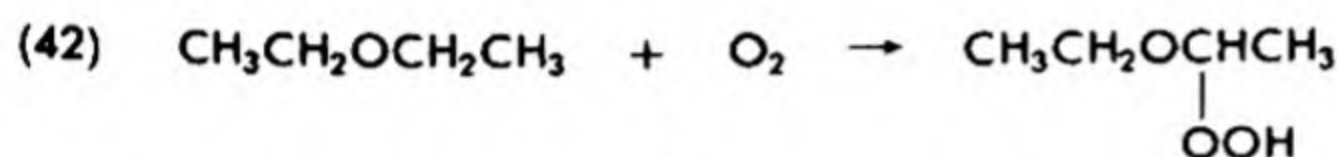
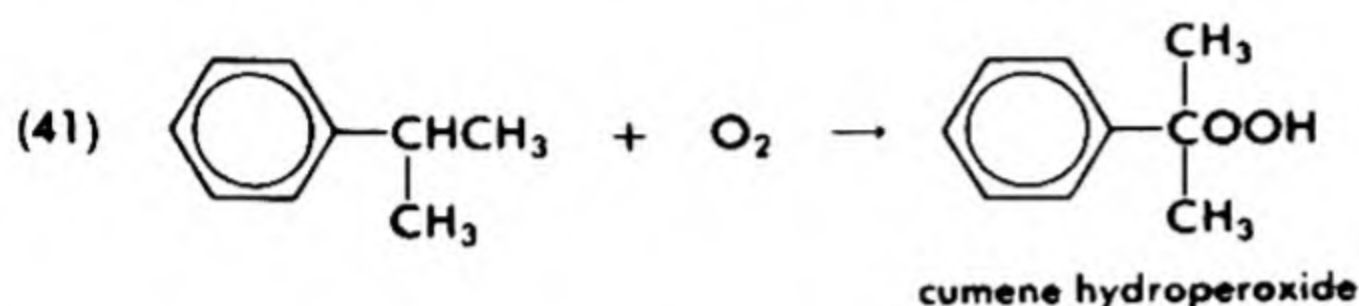
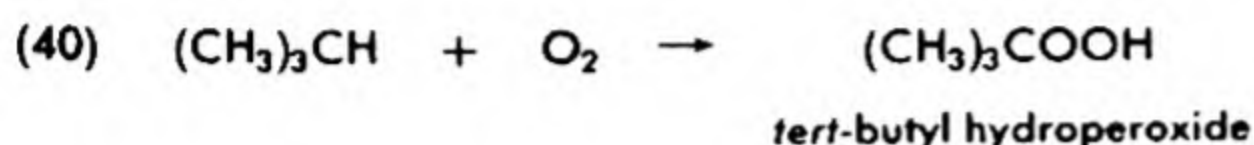
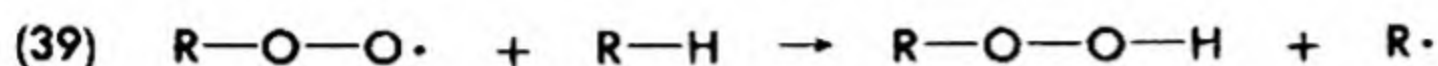
oxygen molecule

this is that, although oxygen is too stable to react rapidly at room temperature with most paired electron systems, it does react rapidly with many free radicals, in particular with alkyl free radicals, where stable hydroperoxy free radicals can be formed (eqs. 6 and 38). Since the reac-



tion shown in eq. (38) is very fast, and the hydroperoxy radicals are relatively inert toward many species, such as chlorine, many free radical reactions are slowed down, or *inhibited*, by traces of oxygen. However, if a relatively reactive carbon-hydrogen bond is present in a compound, the hydroperoxy radical attacks that hydrogen to regenerate the radical $\text{R}\cdot$ and to give a hydroperoxide (eq. 39). Such reaction paths are involved in

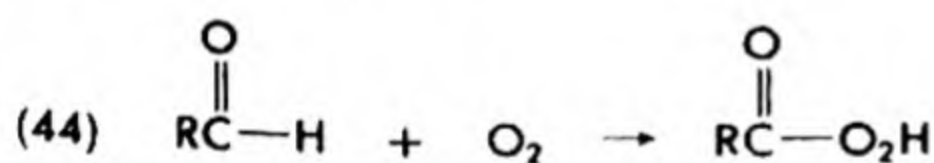
the formation of *tert*-butyl hydroperoxide from isobutane (eq. 40), cumene hydroperoxide from cumene (eq. 41), and the explosive "peroxides" found in aged ether samples (eq. 42). As such reactions are initiated



by radical producers, which the hydroperoxides themselves are when they undergo thermal or photochemical decomposition (eq. 43), such reactions are autocatalytic. When compounds which readily undergo autocatalytic oxidation are involved, the phenomenon is called *autoxidation*.

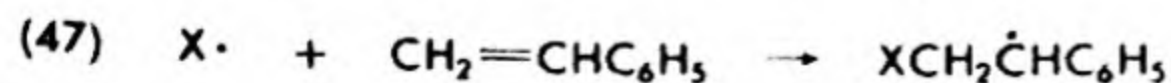
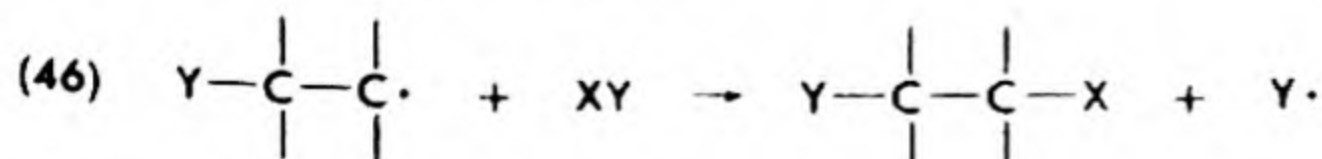


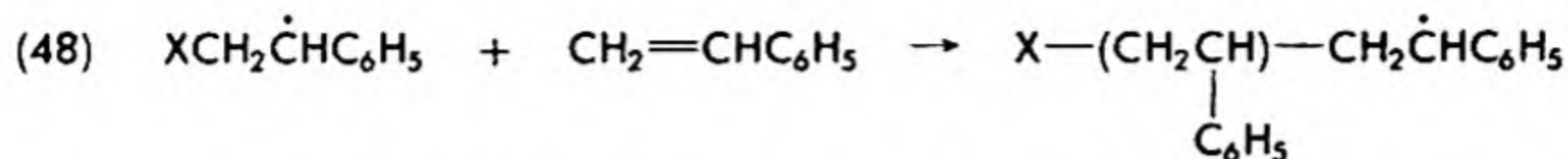
An example which is both industrially important and troublesome, depending on whether one wishes to produce acid or aldehyde, is shown in eqs. (44) and (45).



D. Free Radical Polymerization

In the absence of a good chain transfer agent such that eq. (46) is not favored, addition of a radical to a reactive olefin (eq. 24) may be followed by many repetitions of eq. (24) to build a long polymer chain. Thus, polystyrene is formed from styrene. The model steps in the chain are indicated in eqs. (47) and (48).

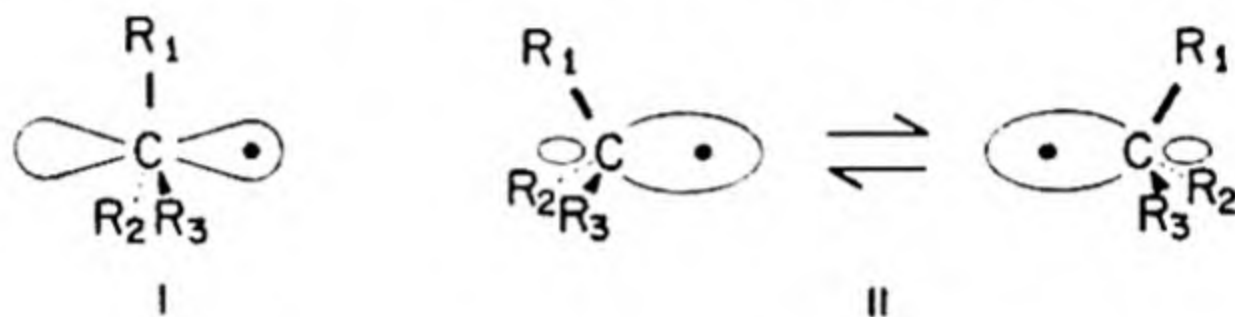




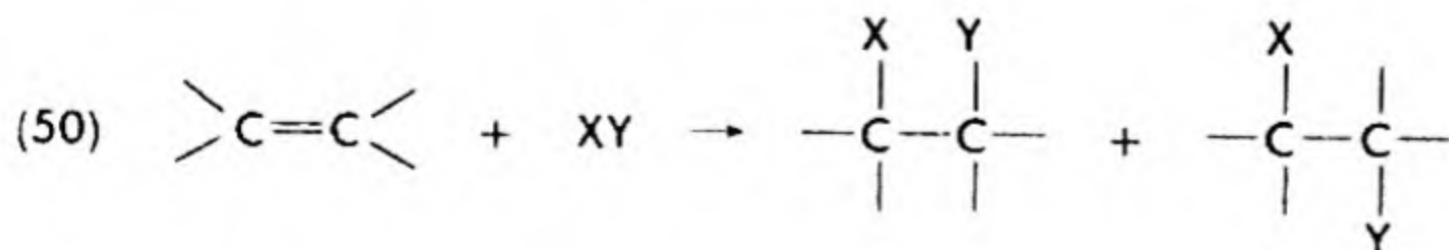
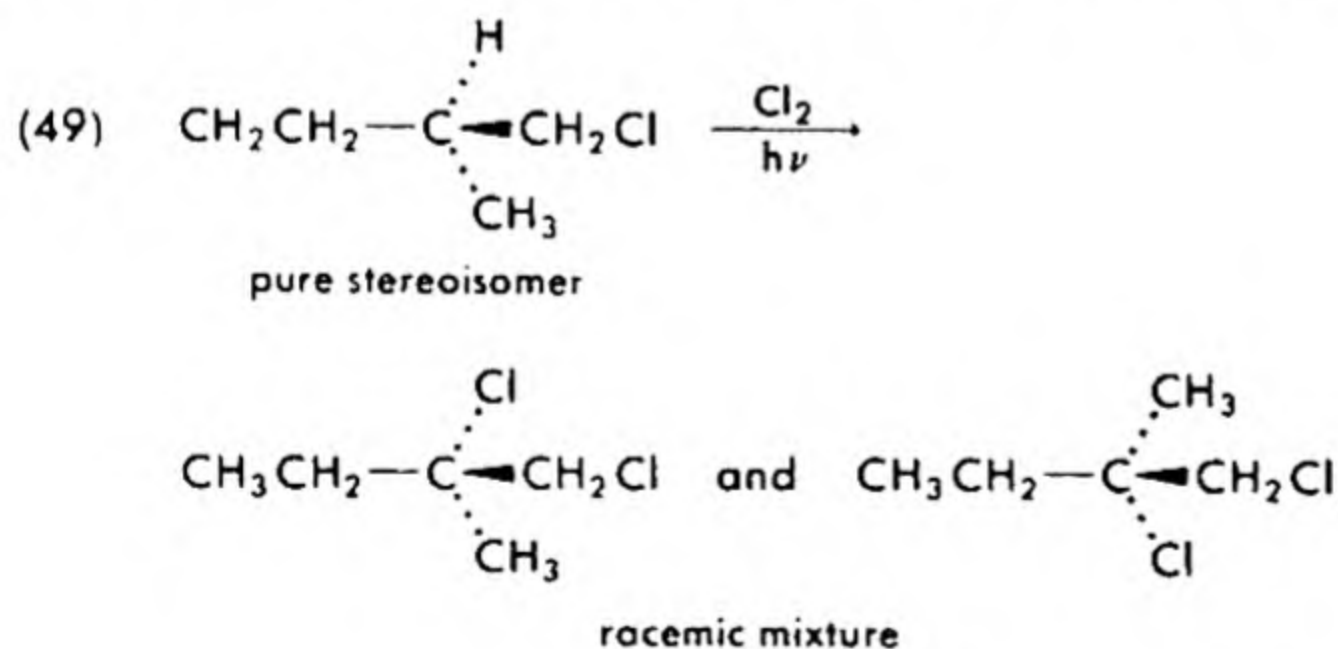
The molecular weight of the polymer depends upon the relative rates of chain propagation (eq. 48) and termination steps and chain-transfer steps. Polymerization is discussed in detail in Chapter 46.

26-5 STEREOCHEMISTRY IN FREE RADICAL REACTIONS

The best pictures of carbon free radicals indicate that at normal or elevated temperatures they are either planar species with the odd electron in a p orbital, I, or rapidly inverting pyramidal species, II. In either case, such species cannot lead to products with maintained configurations or totally inverted configurations. A consequence of this is that radical



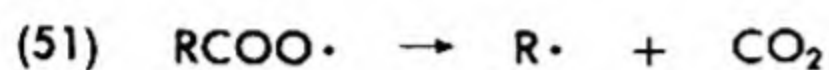
displacement at optically active centers leads to racemic products. For example (outline 49), chlorination of *active*-amyl chloride gives *racemic*-1,2-dichloro-2-methylbutane. Similarly, additions to olefins are ordinarily not cleanly *cis* or *trans*, but instead give both varieties (eq. 50). Thus, with acyclic olefins, both *DL* and *meso* (or *threo* and *erythro*) isomers result.



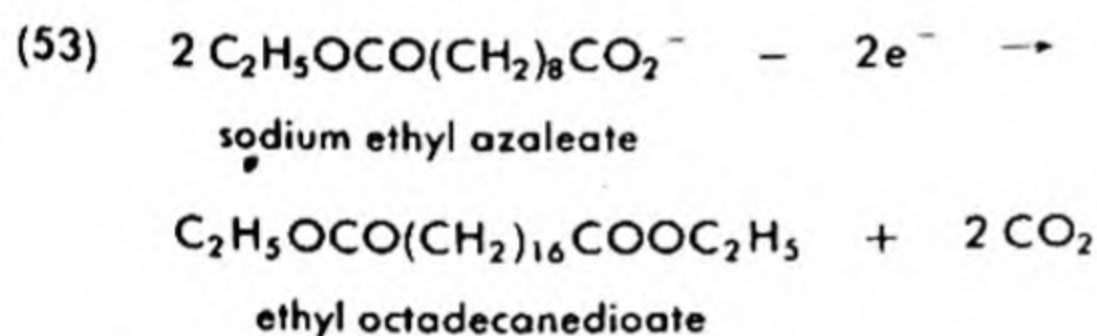
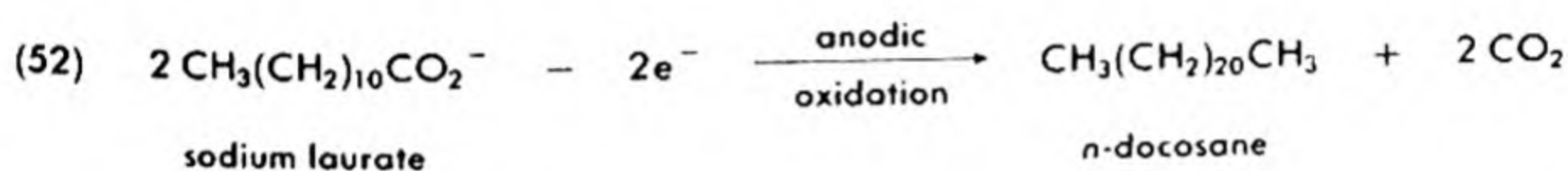
26-6 FRAGMENTATION OF FREE RADICALS

Still another fate available to radicals is loss of a stable molecule with attendant formation of a new radical. Such paths are utilized in many im-

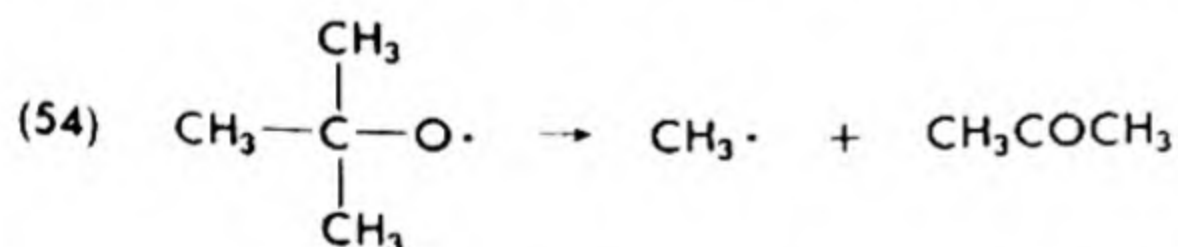
portant reactions. Acyloxy radicals, formed either by decomposition of an acyl peroxide (eqs. 12, 13, and 14) or by electrolytic oxidation of a carboxylate salt (eq. 19), lose carbon dioxide very rapidly to give alkyl or aryl free radicals (eq. 51). One result of this reaction is that initiation of chains with acyl peroxides leads in some cases to incorporation of $\text{RCO}_2\cdot$ and in some to incorporation of $\text{R}\cdot$.



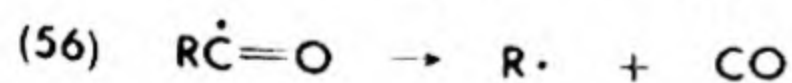
A very important consequence of eq. (51) is seen in the *Kolbe synthesis*, which involves the formation of acyloxy radicals by anodic oxidation, loss of CO_2 to give alkyl radicals, and dimerization of these radicals (eq. 21). The net result of these can be the formation of hydrocarbons from salts of monocarboxylic acids (eq. 52) or the formation of esters of large dicarboxylic acids from salts of half esters of shorter dicarboxylic acids (eq. 53).



Alkoxy radicals may also fragment to give alkyl radicals and carbonyl compounds. Thus at high temperatures, *t*-butoxy radical gives acetone and methyl radicals (eq. 54). Loss of carbon monoxide from acyl radicals



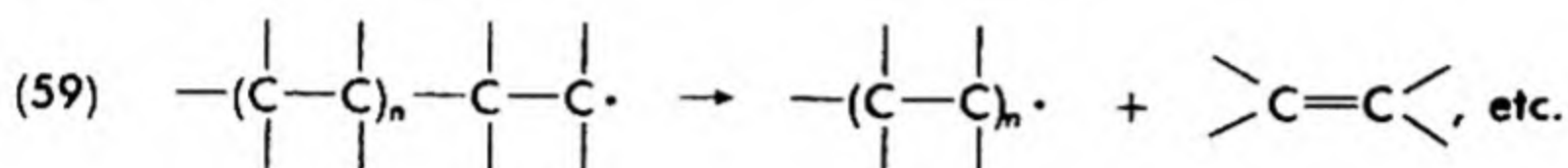
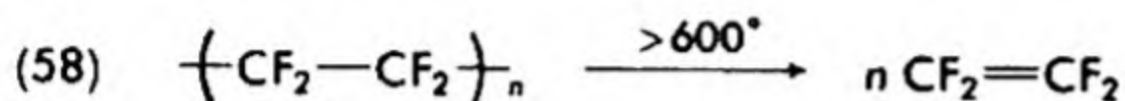
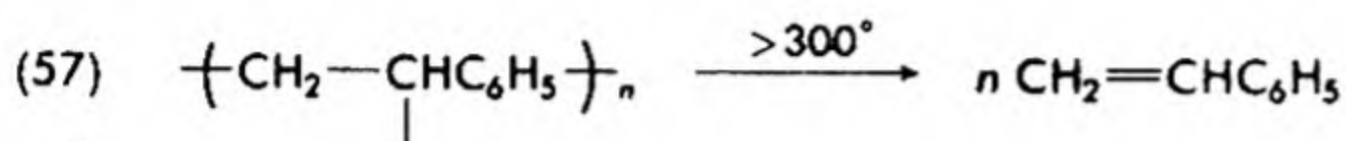
occurs readily at temperatures around 200° . This process leads to chain *decarbonylation of aldehydes* (eqs. 55 and 56).



The reverse of eq. (56) occurs at low temperatures and high carbon monoxide pressures so that copolymers of olefins and carbon monoxide may form in radical polymerization.

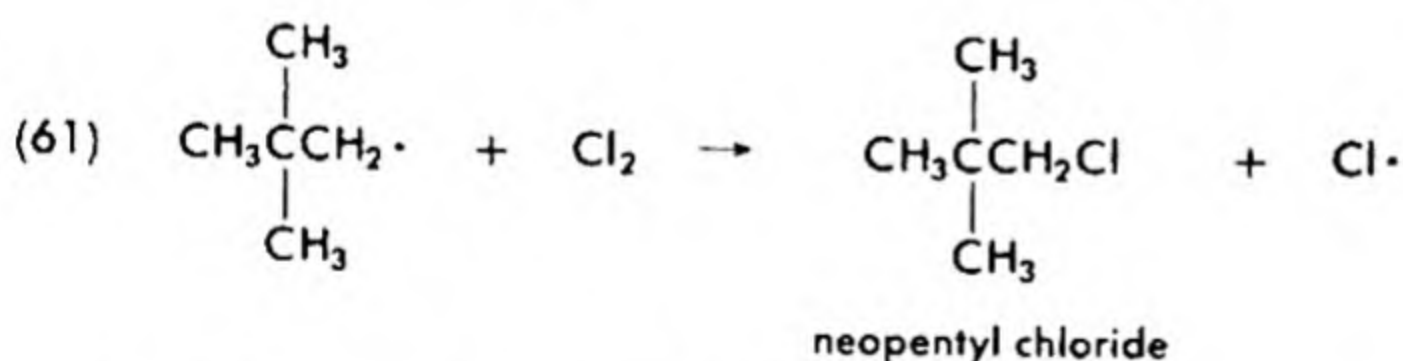
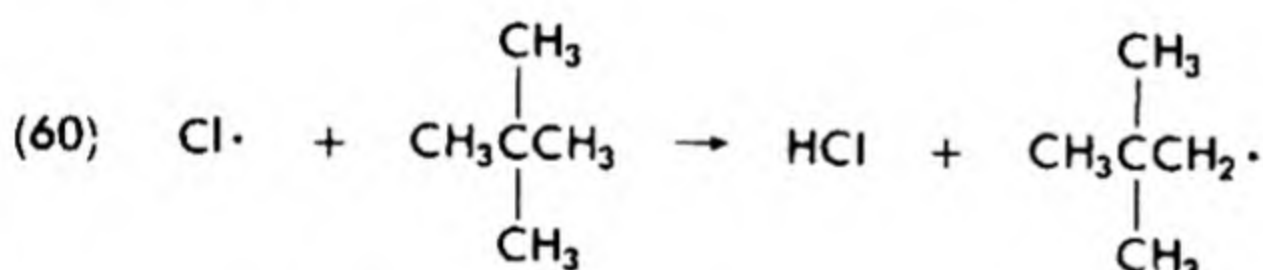
Depolymerization or cracking also occurs at high temperatures where fragmentation of thermally produced radicals gives olefin monomeric

products. Thus, polystyrene gives styrene on heating (eq. 57), and teflon gives tetrafluoroethylene (eq. 58). The key to these cracking reactions is the loss of olefin molecules in a long chain of individual steps represented by eq. (59). This reaction is the reverse of eq. (48).

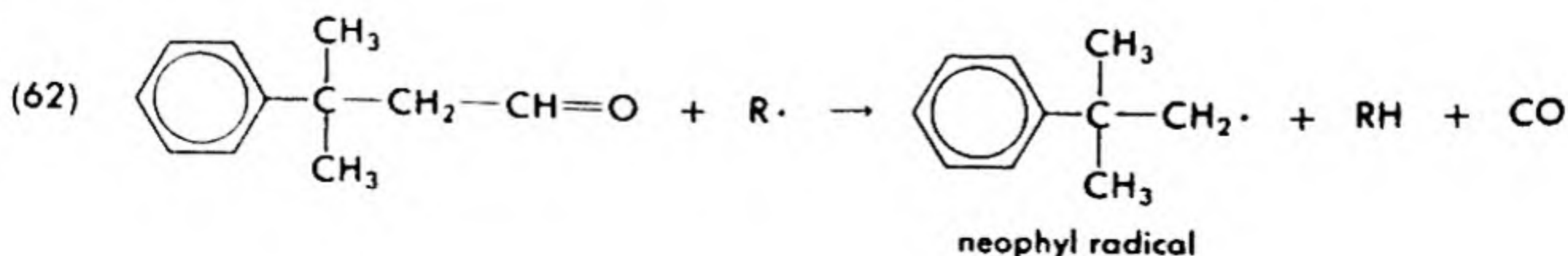


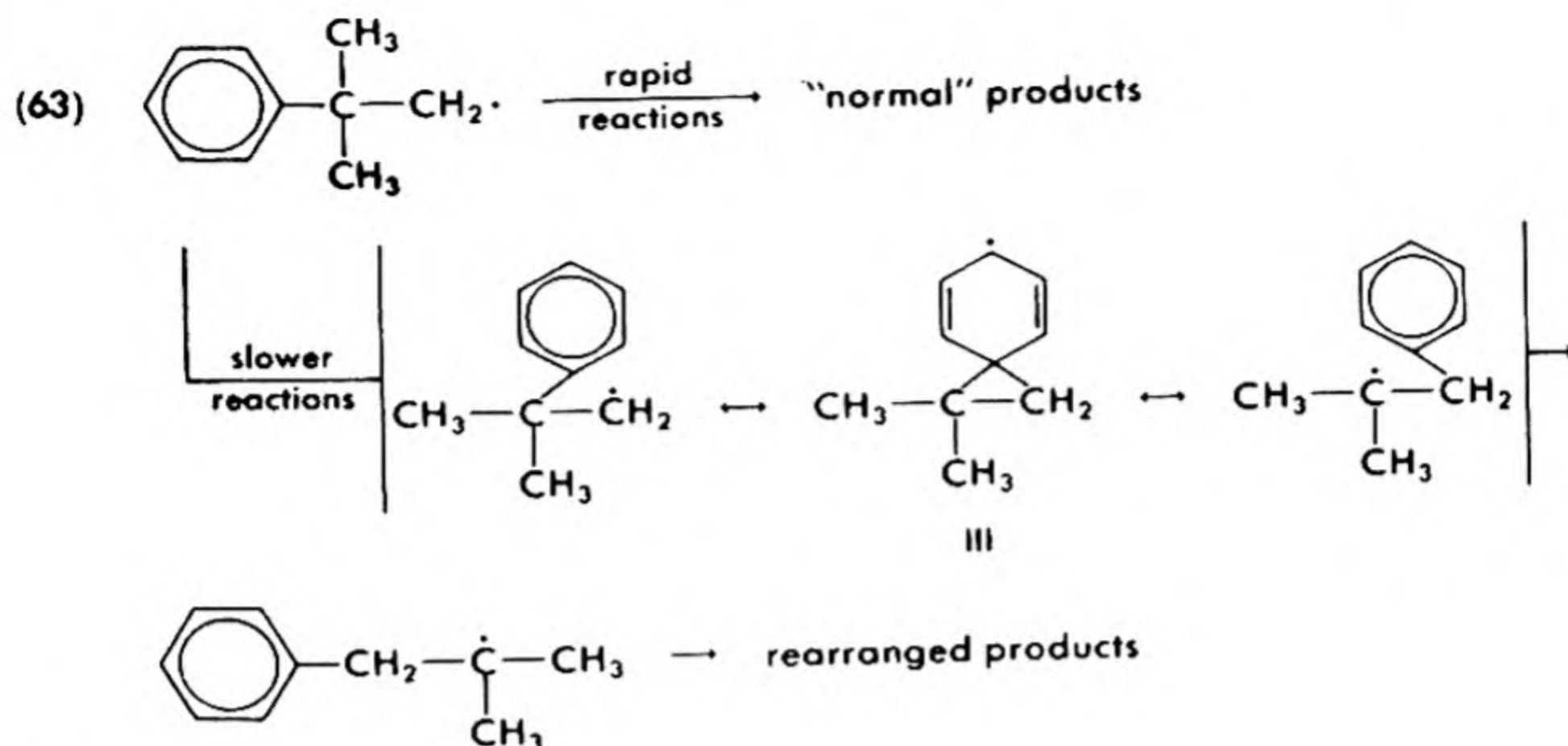
26-7 FREE RADICAL REARRANGEMENTS

Although free radical rearrangements are known, they do not occur as readily as the corresponding carbonium ion rearrangements. Even the neopentyl radical is reasonably stable, although the neopentyl cation (§12-2D(1)) rearranges completely to *tert*-amyl. Thus, chlorination of neopentane gives neopentyl chloride and *not tert*-amyl chloride (eqs. 60 and 61).



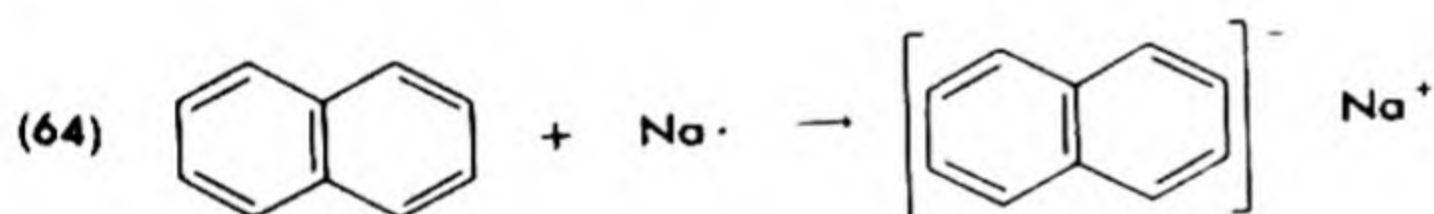
One now well-known free radical rearrangement is that of the "neophyl" (2-phenyl-2-methylpropyl) radical. A notable feature of this rearrangement is phenyl group migration to give a new radical *less stable* than would be obtained by methyl group migration. This is another example of kinetic control giving a less stable product. The transition state, III, for the rearrangement is similar to that of homolytic aromatic substitution.





26-8 RADICAL IONS

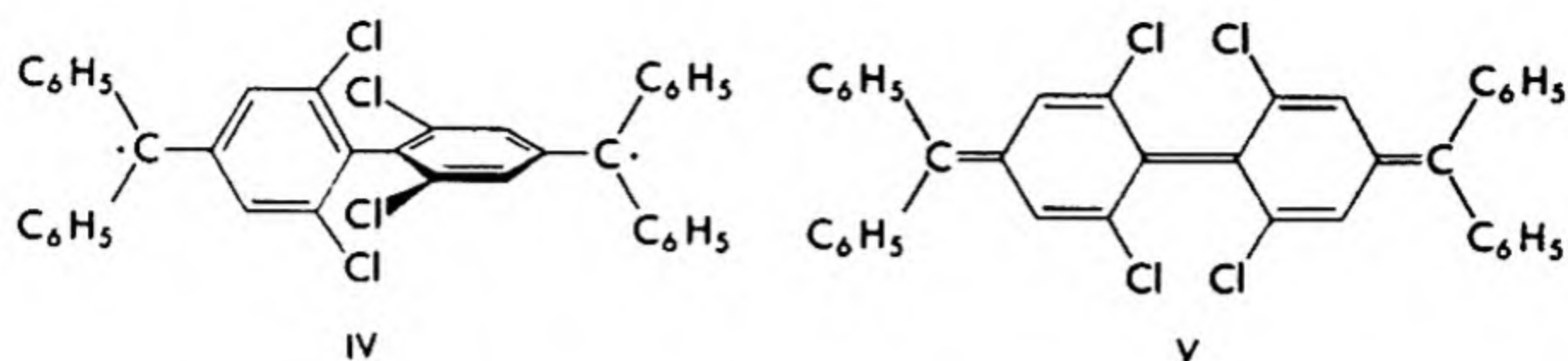
The radicals discussed thus far have been electrically neutral species. However, radicals can have positive or negative charges. In particular, *radical anions*, prepared by addition of sodium to polynuclear aromatic compounds, are of considerable importance in anionic polymerization reactions (§46-1A(3)). The odd electron is transferred to the aromatic compound by the sodium to form a highly colored and highly reactive species. An example of this is seen in the reaction of naphthalene (eq. 64).



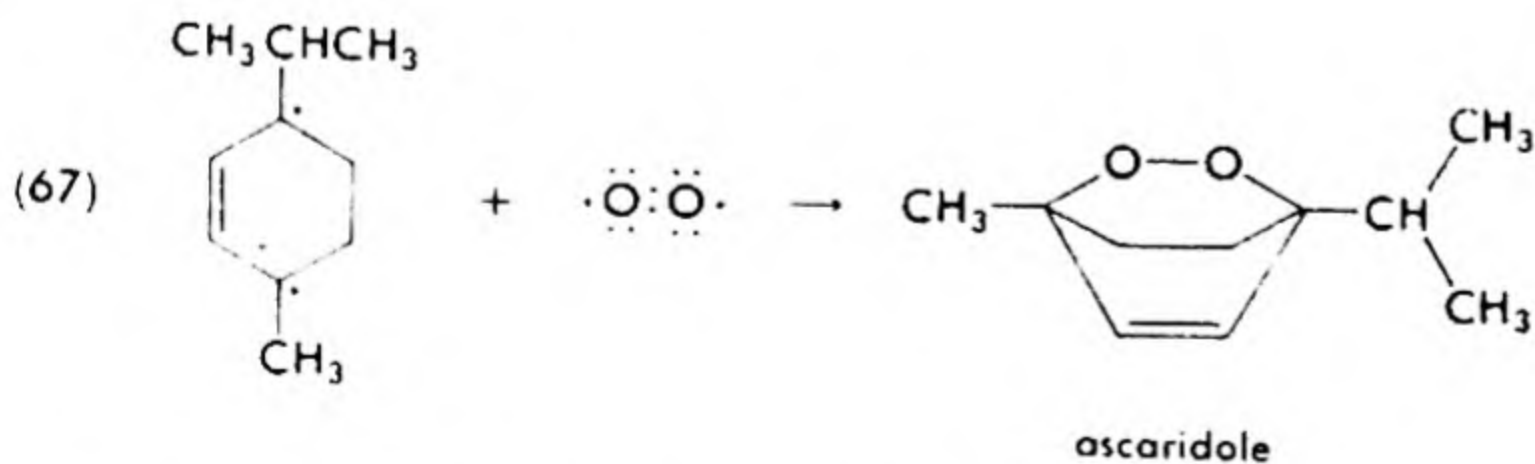
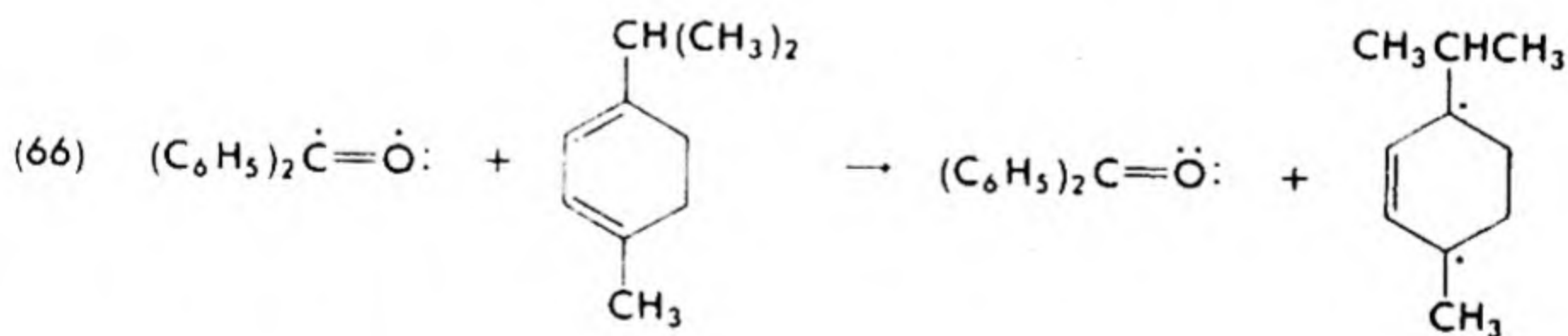
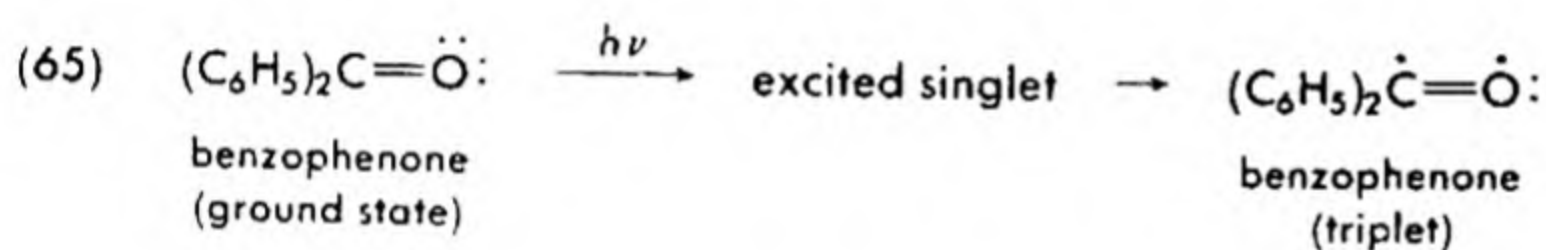
In this radical ion, the electron is in a delocalized orbital (first antibonding) with distribution throughout the carbon skeleton.

26-9 DIRADICALS

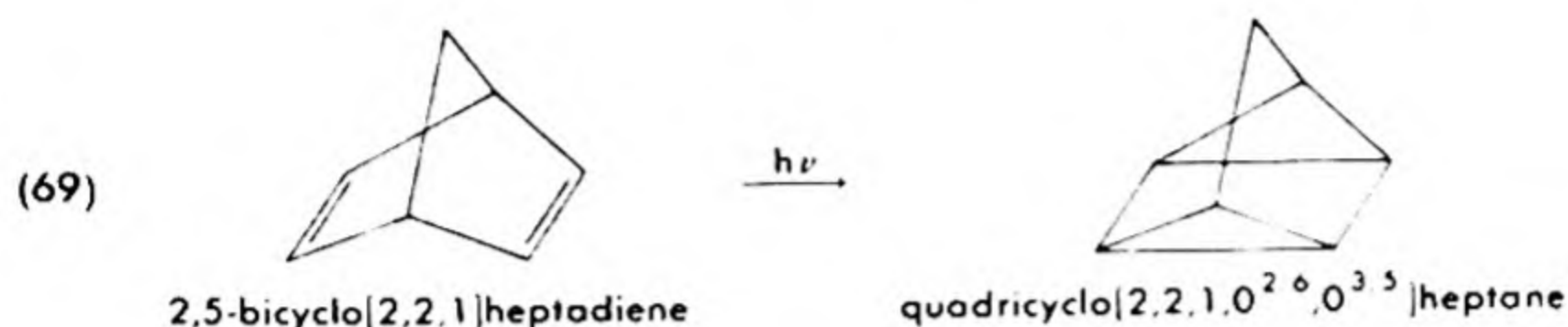
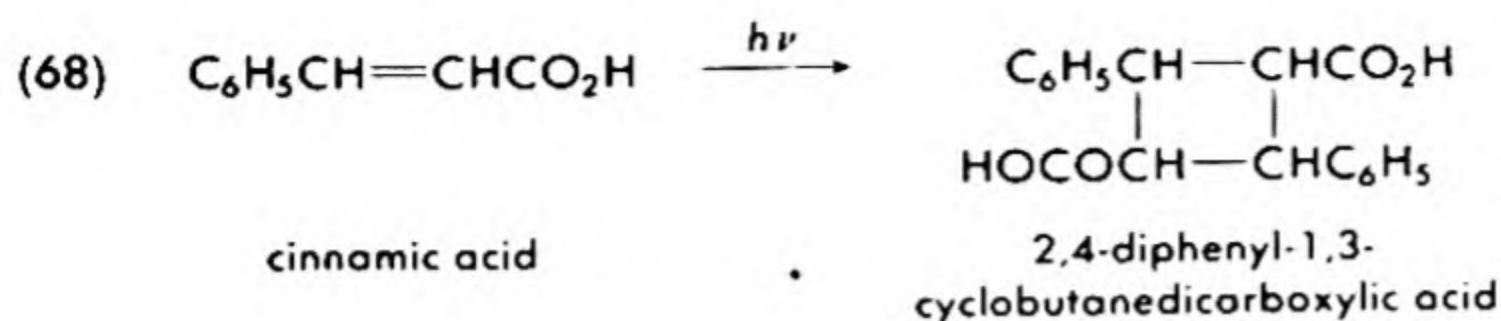
Certain molecules, which have two available molecular orbitals of equivalent energy and two electrons, are more stable with an unpaired electron in each orbital than with paired electrons in one orbital. For example, oxygen (§26-4C(2)) has two unpaired electrons in its ground state (its normal, lowest energy state) and is therefore a diradical. Certain unusual organic molecules also have low-energy diradical structures, for example, IV. This is kept in the diradical form rather than the paired quinoid form, V, by steric interference between the chlorine atoms. The molecule would have to be coplanar to maintain conjugation between the rings.



A number of excited diradicals can be produced photochemically from substances with ground-state paired (singlet) structures (§33-3). Light absorption raises one electron from a ground state orbital to a higher energy MO to form a new higher-energy singlet, in which the spins of electrons remain antiparallel ($n \rightarrow \pi^*$ transition, §9-2A). Often (particularly with carbonyl compounds), these singlets readily cross over to triplet (parallel-spin) diradical states. These can unpair electrons in π systems of other molecules to lead to new diradicals which may undergo reactions characteristic of diradical systems. This is called *photosensitization*, as observed in the formation of ascaridole from α -terpinene (eqs. 65-67). By such means, light of relatively long wavelength can be used to peroxidize dienes and anthracenes. Many dyes can be used as photosensitizers.

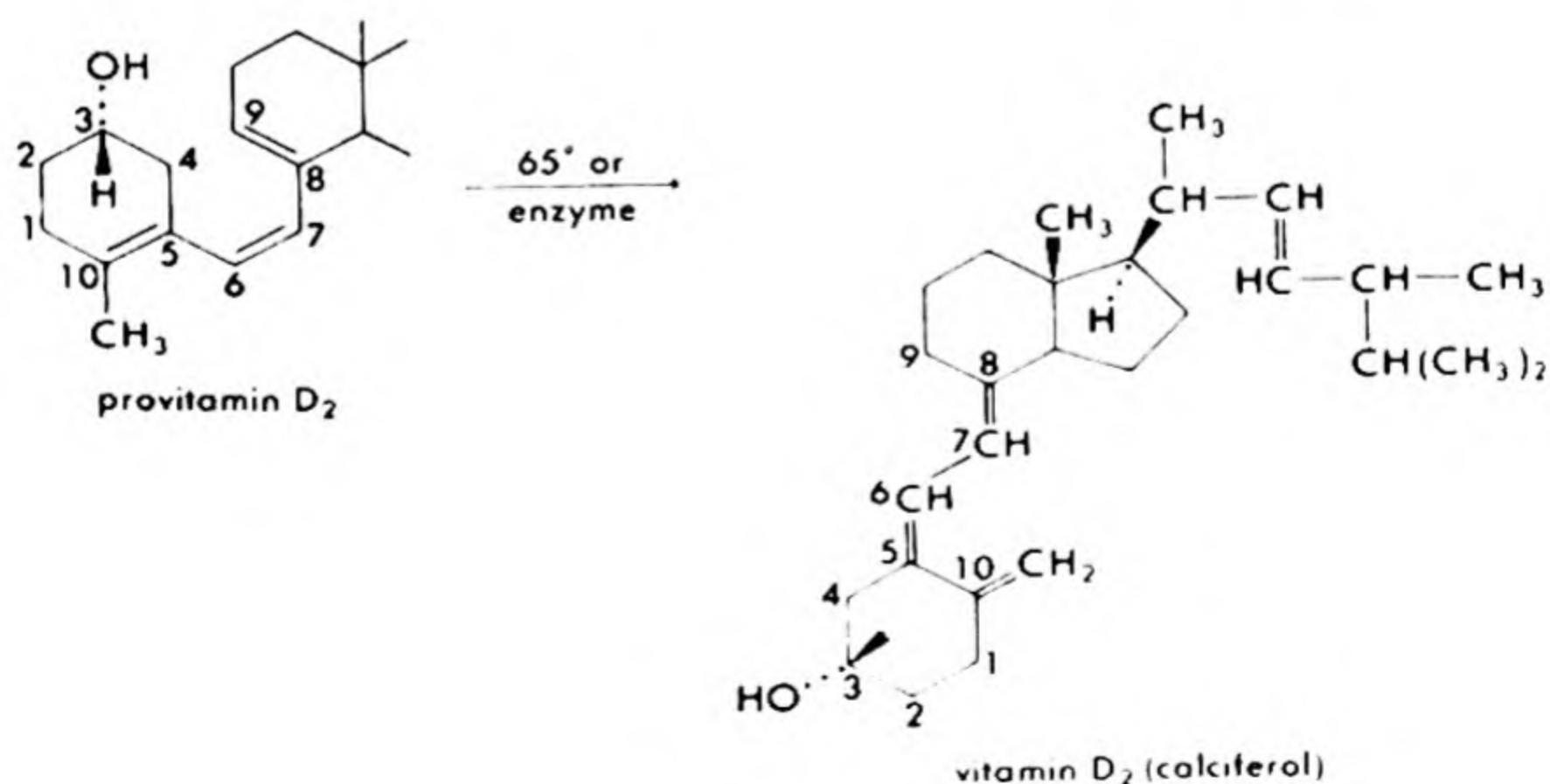
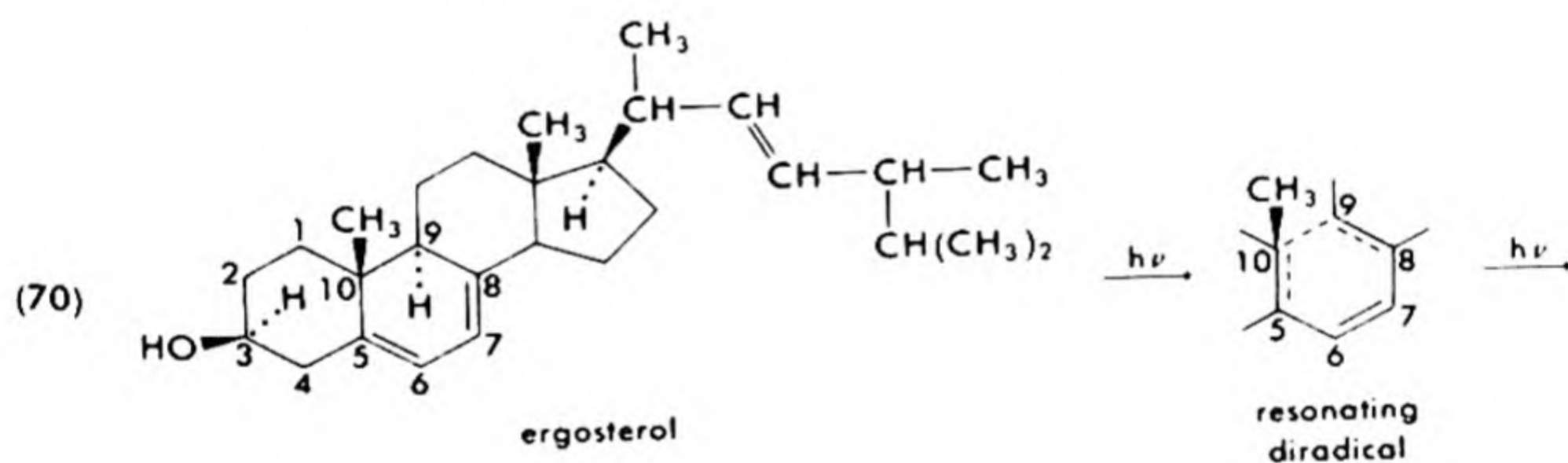


The formation of four-membered rings by irradiation of olefins, either with or without photosensitization, is a very common reaction. These involve triplet diradical intermediates. Some examples are given in eqs. (68) and (69).



One should note that such reactions are not chain reactions and that only one molecule is activated per quantum of light.

Another type of reaction possibly involving a diradical intermediate is exemplified by the ring cleavage of ergosterol upon irradiation with near ultraviolet radiation (outline 70).



SUPPLEMENTARY READINGS

- Gould, E. S., *Mechanism and Structure in Organic Chemistry*, Holt-Dryden, New York, 1959, Chapter 16.
- Hine, J., *Physical Organic Chemistry*, 2nd Ed., McGraw-Hill, New York, 1962, Chapters 18-23.
- Stacey, F. W., and J. F. Harris, Jr., "Formation of Carbon-Hetero Atom Bonds by Free Radical Chain Additions to Carbon-Carbon Multiple Bonds," *Org. Reactions*, **13**, 150-376 (1963).
- Walling, C., *Free Radicals in Solution*, Wiley, New York, 1957.
- Walling, C., and E. S. Huyser, "Free Radical Additions to Olefins to Form Carbon-Carbon Bonds," *Org. Reactions*, **13**, 91-149 (1963).

QUESTIONS AND PROBLEMS

1. Write formulas or equations to illustrate the following concepts. Provide verbal explanation of each illustration.

- | | |
|----------------------|------------------------|
| a. autoxidation | g. initiator |
| b. chain propagation | h. photosensitizer |
| c. chain transfer | i. quantum yield |
| d. diradical | j. stable free radical |
| e. inhibitor | k. termination |
| f. initiation | l. triplet state |

2. Write equations for the reactions which occur between substances as indicated below. Indicate essential special conditions.

- | | |
|---|--|
| a. propylene in carbon tetrachloride + <i>t</i> -butyl peroxide | d. methyl acrylate (liquid) + benzophenone in UV light |
| b. liquid propylene + <i>t</i> -butyl peroxide (Note: propylene does <i>not</i> polymerize readily by free radical chains.) | e. benzaldehyde + O ₂ rapidly bubbled through |
| c. methyl acrylate (liquid) + <i>t</i> -butyl peroxide | f. benzaldehyde + air (open beaker, bottle, etc.) |
| | g. benzophenone + excess 2-propanol in sunlight |
| | h. bornane + O ₂ + Cu ⁺ |

3. Show how the following syntheses can be effected satisfactorily. Indicate necessary inorganic reagents, initiators, and special conditions.

- | | |
|---|--|
| a. 1,2,3,4-tetraphenylcyclobutane from the appropriate olefin | c. polyacrylonitrile from acetaldehyde |
| b. 3-bromo-1,1,1-trichlorobutane from isopropyl alcohol | d. cumene hydroperoxide from benzene and propylene |
| | e. sebacic acid from adipic acid |

4. Suggest explanations for the following phenomena, based on the relative stabilities of reactive intermediates and/or transition states.

a. Peroxide-catalyzed addition of hydrogen bromide to unsymmetrical olefins occurs in a direction opposite to that of the acid-catalyzed addition.

b. Homolytic substitution by phenyl radicals from benzoyl peroxide into nitrobenzene occurs *ortho* and *para* to the nitro group, and much *more* readily than similar substitution into benzene, whereas electrophilic substitution of nitronium ions into nitrobenzene occurs *meta* to the nitro group, and much *less* readily than into benzene. (Both processes occur by initial addition of the reagent.)

27

Oxidation

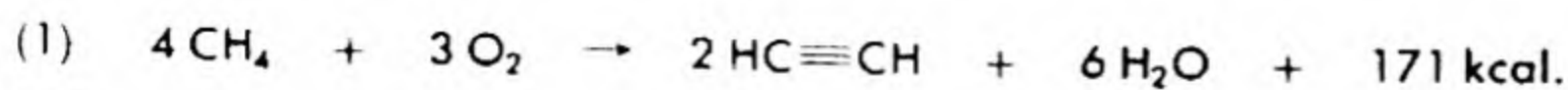
27-1 OXIDATION BY AIR AND OXYGEN

Oxidation by the several forms of elementary oxygen is, like hydrogenation, a field warranting separate treatment. The aspects of oxidation range from controlled reactions giving definite increments of oxidation at specific functional groups through combustion to explosions. Also considered briefly, though not involving oxygen as the element, is detonation.

A. Combustion, Explosion, and Detonation

The differences between combustion, explosion, and detonation are largely in rate, although significant differences in mechanism may also appear. Combustion is a more or less moderate reaction which produces a luminous or slightly luminous flame. The reaction takes place at a measurable rate. Combustion in ample air or oxygen under conditions of good mixing generally produces completely oxidized products such as carbon dioxide and water. In limited oxygen, or when mixing is poor, or when the reaction is quenched by sudden cooling, carbon black, and such compounds as acetylene, alcohols, formaldehyde, other aldehydes, ketones, acids, and carbon monoxide are formed. The presence of carbon monoxide in combustion gases is a serious hazard in the use of the internal combustion engine and in combating fires.

Some incomplete combustion reactions have commercial importance. Methane, obtained from natural gas and from petroleum cracking gases, is an abundant source of carbon black. The Sachsse process for the manufacture of acetylene consists of a methane burner provided with a water spray for quenching, together with devices for separating the desired products from the exit gases. The engineering design of such processes is critical, as acetylene is thermodynamically unstable at moderate temperatures. The gases must therefore be cooled rapidly from reaction temperature (about 1700°) to room temperature in order to avoid decomposition of the acetylene.

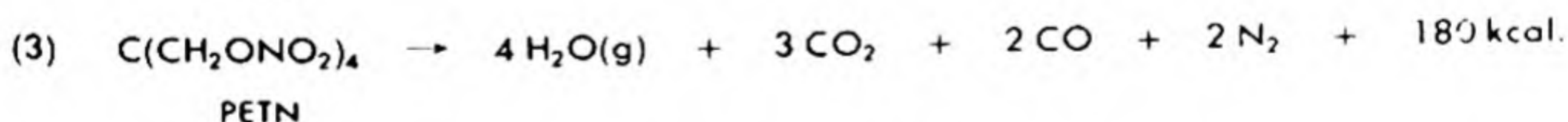
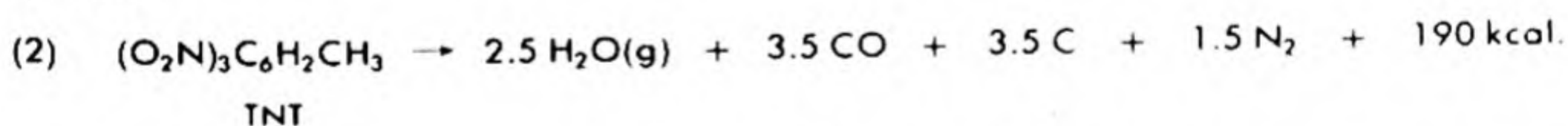


Controlled combustion involves the burning of a fuel-oxidant mixture in such a fashion that the burning wave and the pressure wave that results from the production of heated gases develop in a regular fashion and over a relatively long period of time. In such a situation the expanding gases may do useful work such as driving a piston in an internal combustion engine, propelling a projectile out of a rifle or cannon or driving a jet or rocket motor.

A *detonation* is an uncontrolled combustion. It is propagated by a compression wave which heats the mass to its decomposition temperature as the wave proceeds at approximately the speed of sound through the explosive. Thus, by the time the first shock wave reaches the end of the explosive opposite the initiation point, the entire explosive has decomposed, and the full force of the detonation is behind that one wave. Detonations are useful only in shattering, making holes, or initiating seismological waves.

Highly nitrated compounds, such as trinitrotoluene (TNT), pentaerythritol tetranitrate (PETN), and glycerol trinitrate, are useful high explosives. Certain metal salts, such as mercury fulminate, $\text{Hg}(\text{O}-\text{N}\equiv\text{C})_2$; silver azide, $\text{Ag}(\text{N}=\text{N}=\text{N})$; and silver acetylide, are detonating agents used in blasting caps to set off the less sensitive, more safely handled nitro compounds and nitrate esters.

The most common explosives are compounds which contain both oxidizing and reducing groups in the same molecule. A favorable balance of these groups is such as to give complete transformation to gaseous products. Nitrogen, water, and carbon monoxide are preferred products in a highly exothermic reaction. These are illustrated in eqs. (2) to (4) which show the theoretical behavior of TNT, PETN, and mercury fulminate.



For a high explosive to be useful, it must have a low enough sensitivity to shock so that it can be transported without danger. Glycerol nitrate ("nitroglycerin") is a material of considerable blasting power, but of erratic enough sensitivity to make its use in its normal liquid state very hazardous. Alfred Nobel discovered that it became safe when absorbed in porous solids. Dynamite is diatomaceous earth impregnated with glycerol trinitrate. The plastic mixture produced by mixing cellulose nitrate (gun-

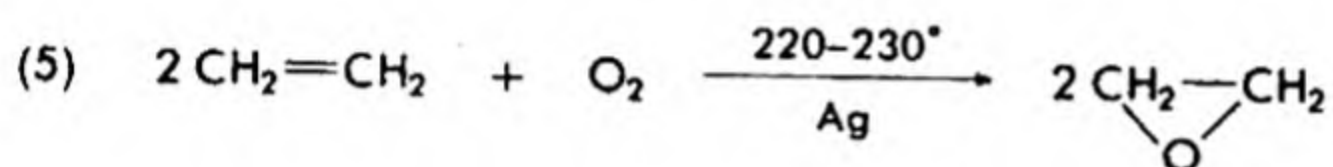
cotton) with glyceryl trinitrate is the base of cordite or smokeless powder, the normal propellant for rifle and cannon ammunition.

While combustion, explosion, and detonation undoubtedly are free radical chain reactions, the chain sequences are very complex, even in the combustion of as simple a compound as methane. Infrared radiation studies of flames from burning methane have revealed the presence of such free radicals as methyl, methylene, atomic hydrogen, and hydroxyl in the thin zone, a few thousandths of a centimeter thick, in which the combustion occurs.

B. Oxidation of Unsaturated Hydrocarbons

Two kinds of gaseous oxidation of unsaturated hydrocarbons are especially important to organic chemistry. One is the industrially important *epoxidation* reaction, and the other a tool which has played a vital role in structural analysis, *ozonolysis*.

Catalytic oxidation of ethylene with air gives fair yields of ethylene oxide (eq. 5). This is not a reaction of general utility for higher epoxides,



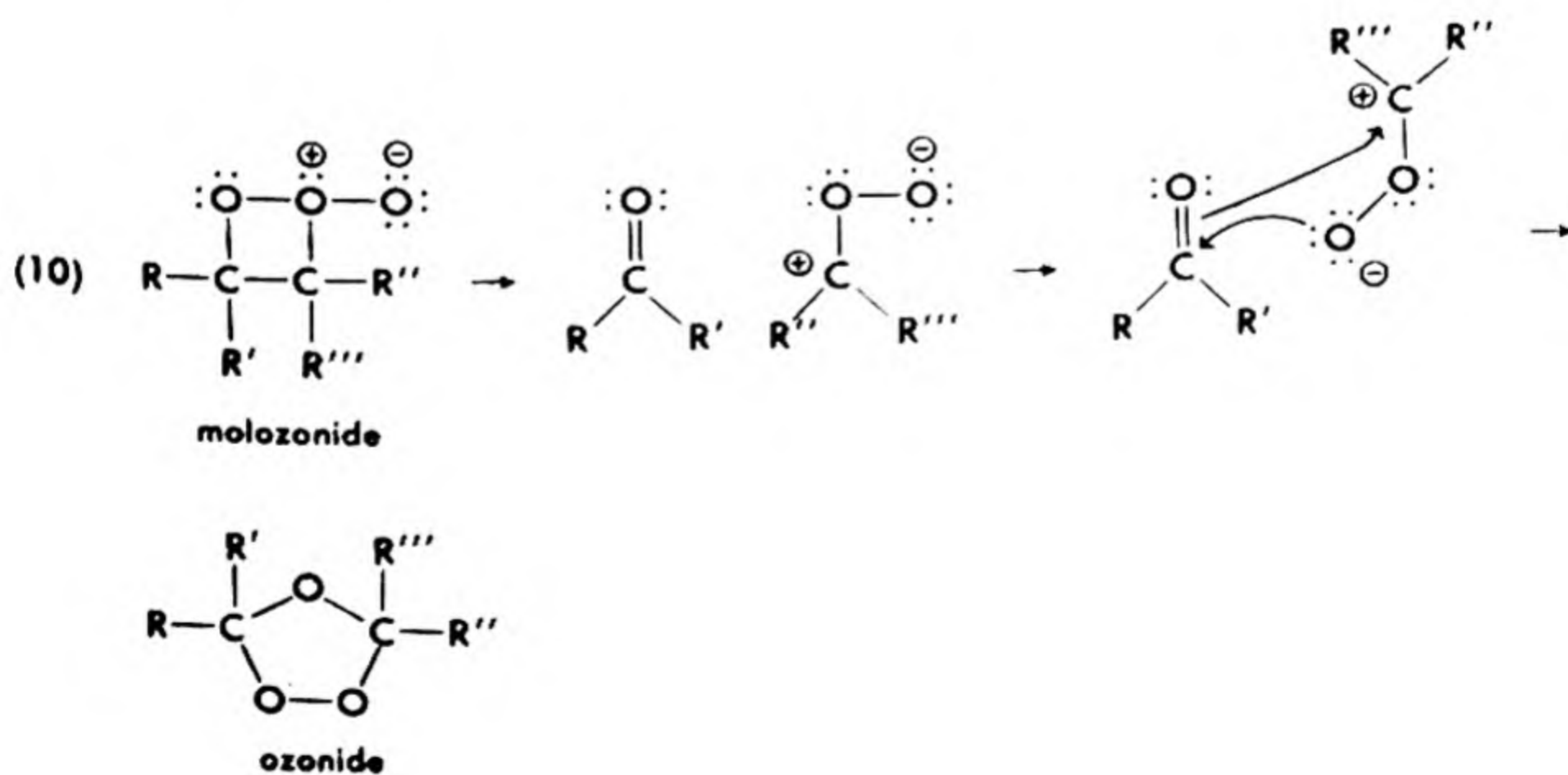
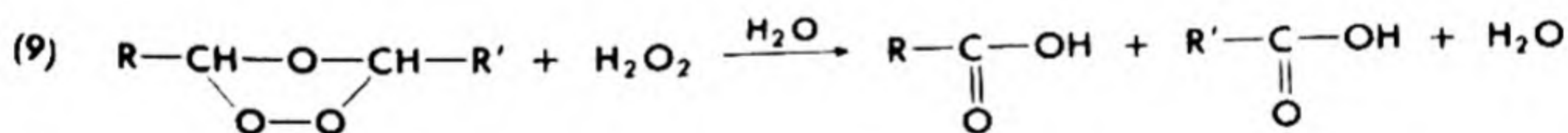
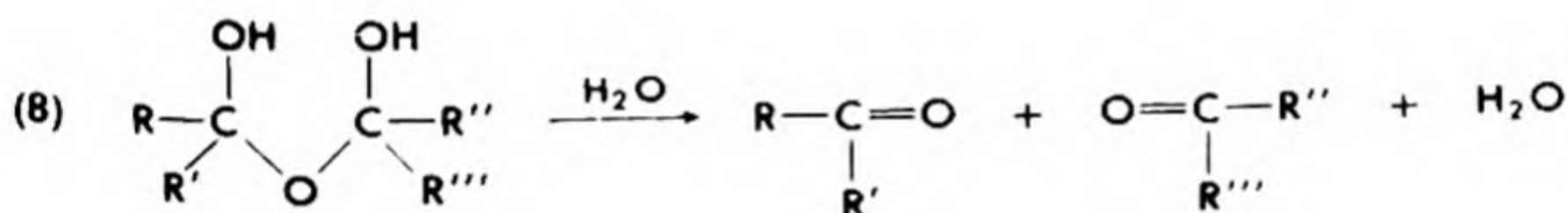
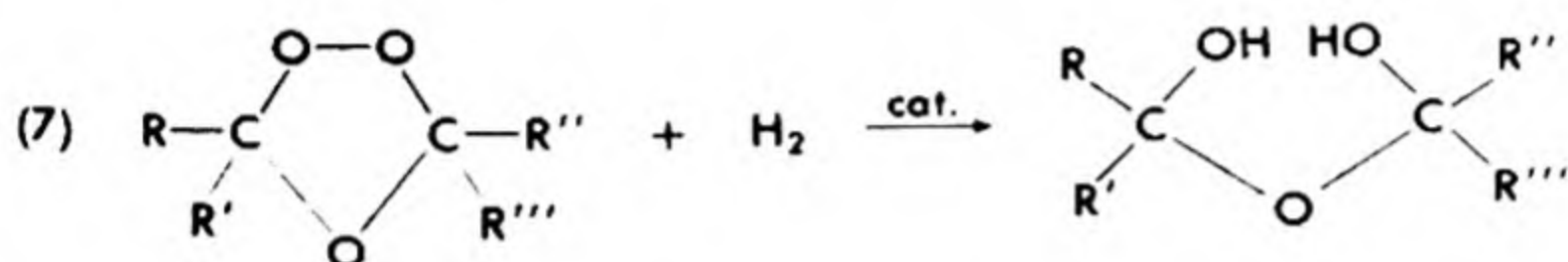
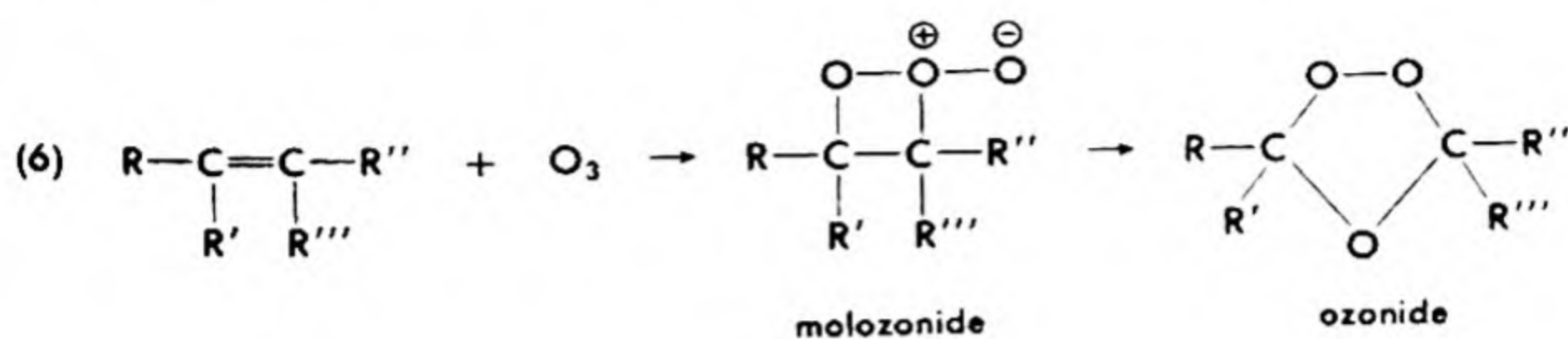
as reactions of allylic hydrogens in higher olefins occur more readily than addition.

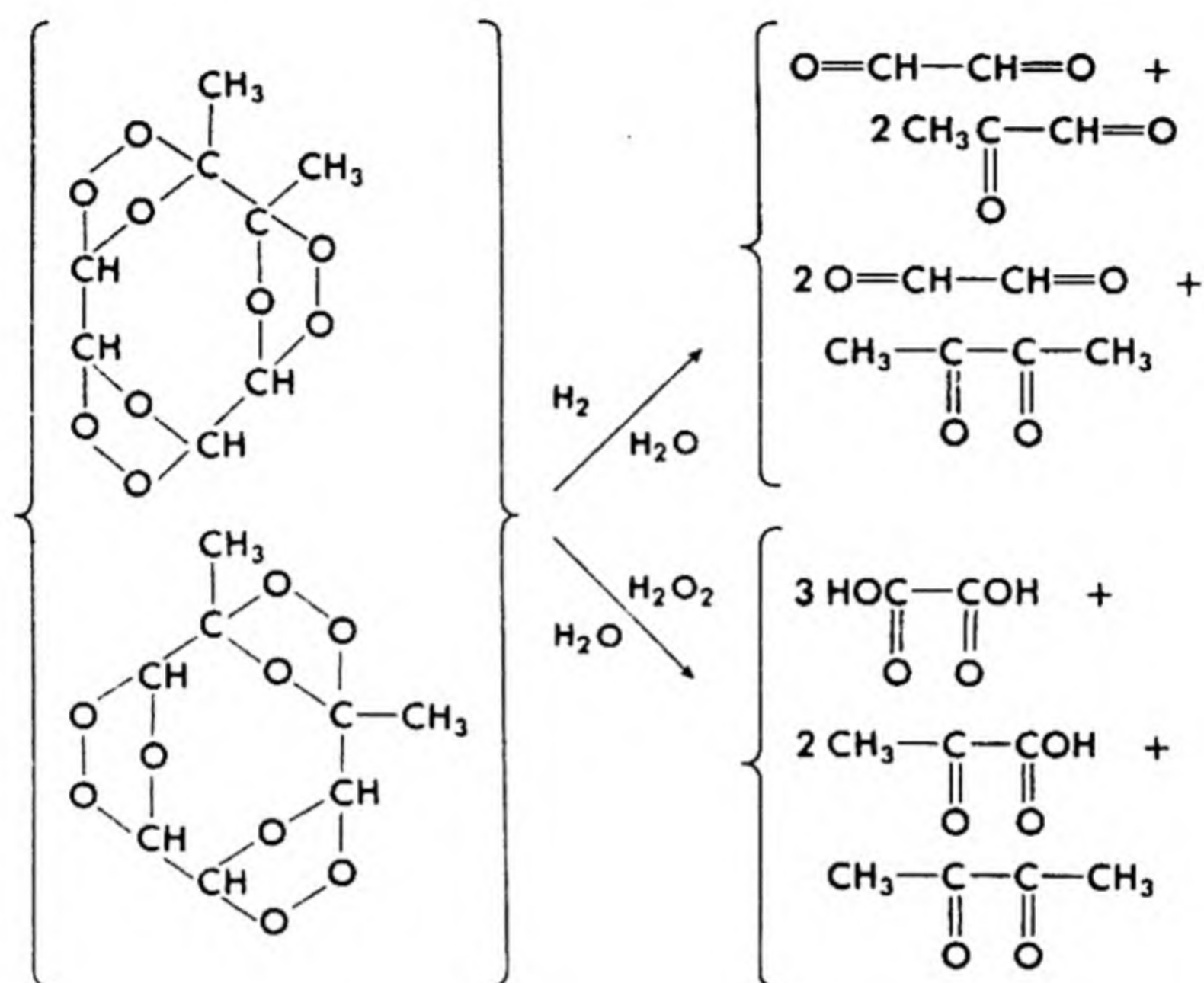
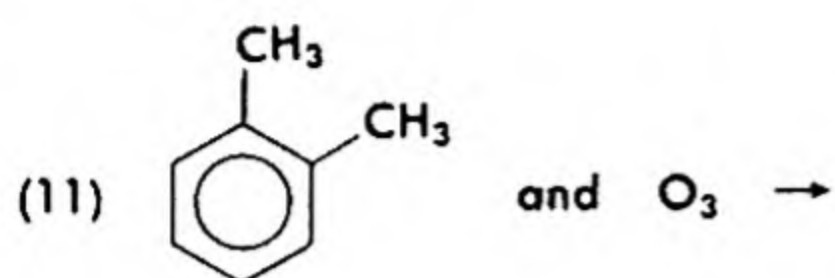
Addition reactions of olefins ordinarily give no simple clue to the position of the double bond. While products of addition might be converted to derivatives, reactions of which could give some indication of the positions of double bonds, the evidence would be indirect and possibly ambiguous or misleading. Ozonolysis provides a means to cleave an olefin, usually cleanly and unambiguously, at its double bond to give fragments which can be identified quite readily.

Ozone for ozonolysis is prepared by passing oxygen through a high voltage, silent electrical discharge tube. The oxygen-ozone mixture is then bubbled through a solution of the alkene or mixed with the alkene vapors. The ozonide, generally an unstable and explosive material, is hydrolyzed in the presence of a reducing agent or an oxidizing agent. Aromatic rings are attacked, but less readily than olefinic bonds; thus, selectivity is observed. Products of both valence bond structures are observed (outline 11).

The products of reductive hydrolysis of the ozonide are aldehydes and ketones. The reduction is effectively carried out by catalytic hydrogenation or by reduction with powdered zinc.

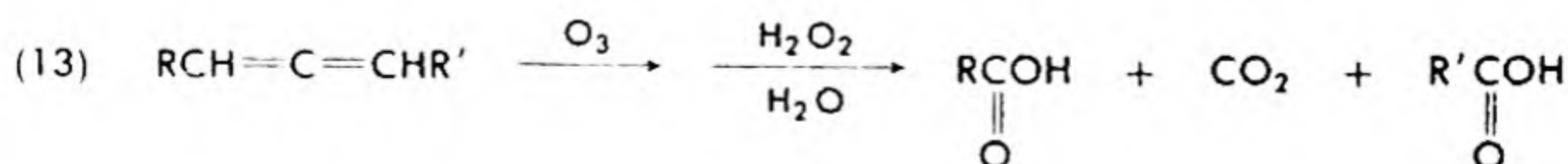
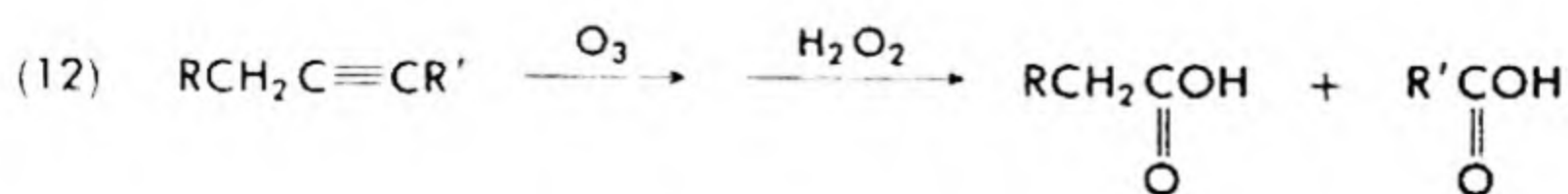
Products of oxidative hydrolysis by hydrogen peroxide solution are carboxylic acids and ketones. The intermediates are called a *molozonide* (unstable) and *ozonide* (relatively stable but explosive when dry), respectively. The path of the rearrangement is given in outline (10).





Occasionally, ozonolysis has proved to be a suitable method for the laboratory or industrial synthesis of an aldehyde, ketone, or carboxylic acid. The main drawback is the danger inherent in handling large amounts of explosive ozonide.

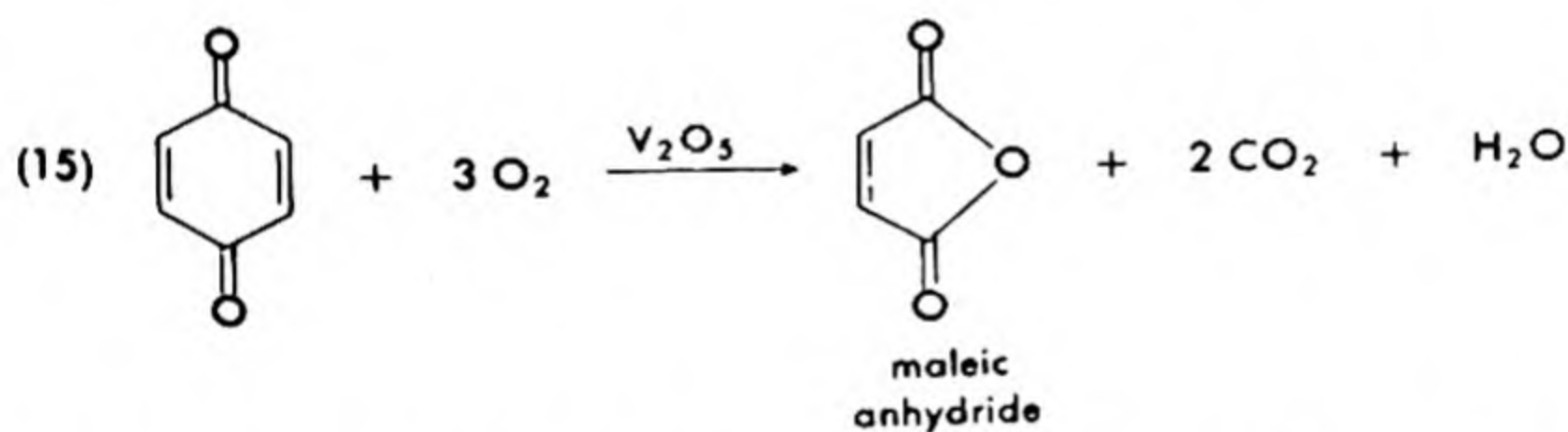
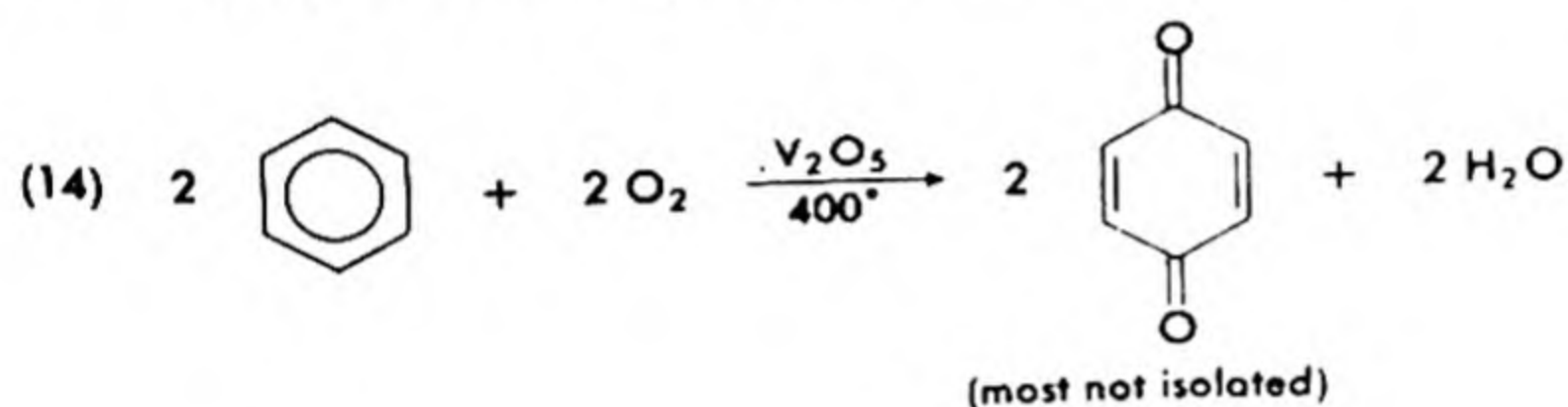
Ozone attacks unsaturated functions other than olefinic and acetylenic linkages, such as aldehyde groups. Saturated groups and less easily oxidized groups such as keto groups are not attacked. Alkynes are readily distinguishable from cumulated alkadienes by ozonolysis, in contrast to results with other oxidizing agents, which often cause isomerization of the allenes in the process of oxidation.



C. Oxidation of Aromatic Nuclei

Nonactivated benzene rings are highly resistant to most oxidative attack. Reagents in solution oxidize aliphatic side chains before disrupting the ring in mononuclear aromatic compounds. Polynuclear compounds, with their less completely stabilized aromatic systems, are more readily oxidized on the rings. Nevertheless, benzene is capable of being oxidized to simpler organic compounds in the presence of certain catalysts and under very careful control of conditions.

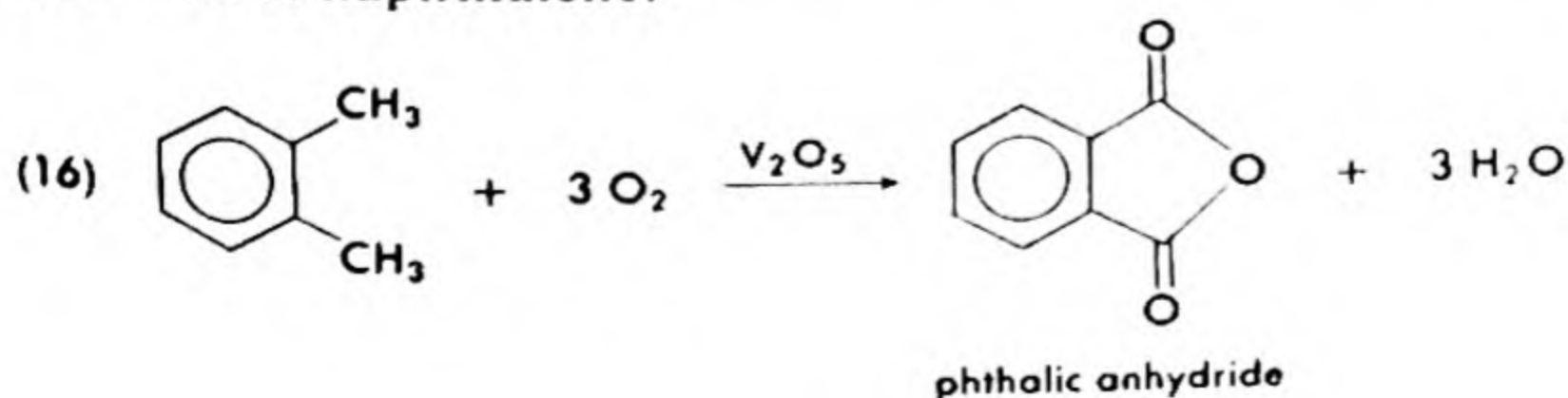
Air oxidation of benzene over vanadium pentoxide gives maleic anhydride and traces of benzoquinone. The presence of the latter suggests that the quinone may be an intermediate in the oxidation. It cannot be obtained in good yield, however, because the quinone is more readily oxidized than the original benzene, and there is no way to remove the quinone rapidly enough to prevent its oxidation.



Oxidation of naphthalene to phthalic anhydride is carried out in the same manner.

D. Oxidation of Aromatic Side Chains

Some commercial processes which involve air oxidation of side chains on aromatic compounds are slowly gaining importance. Preparation of phthalic anhydride by oxidation of *o*-xylene now competes favorably with oxidation of naphthalene.



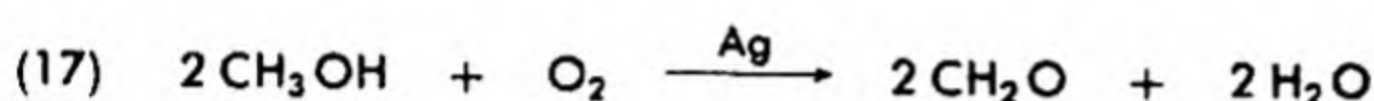
The industrial preparation of hydroperoxides by reaction of air with cumene or with isobutane (§26-4C(2)) has already been discussed.

E. Oxidation of Saturated Hydrocarbons

The partial air oxidation of propane and butane leads to a mixture of alcohols, aldehydes, ketones, and acids largely in the one- to four-carbon range. This process is of industrial significance although difficult problems of separation are involved.

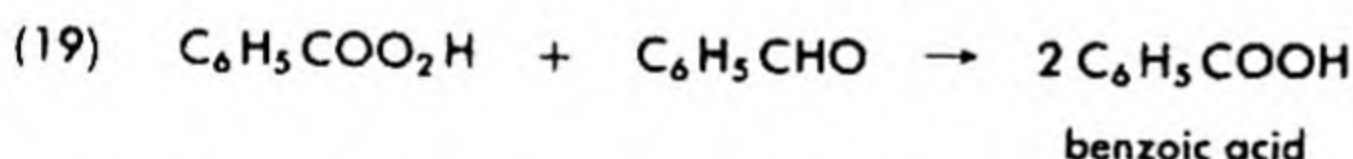
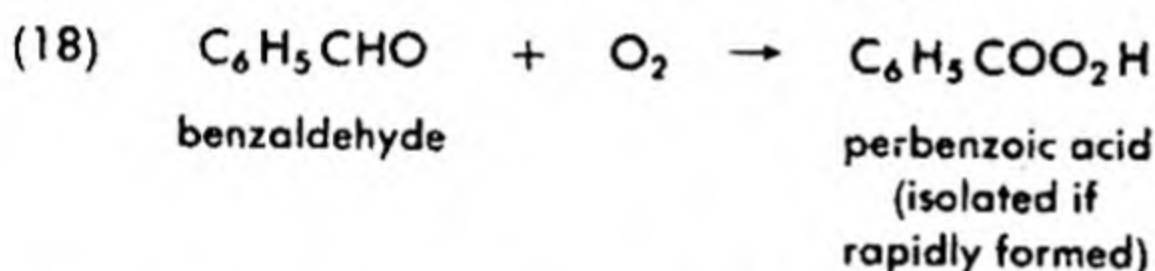
F. Oxidation of Alcohols

The industrial preparation of formaldehyde from methanol is given in eq. (17).

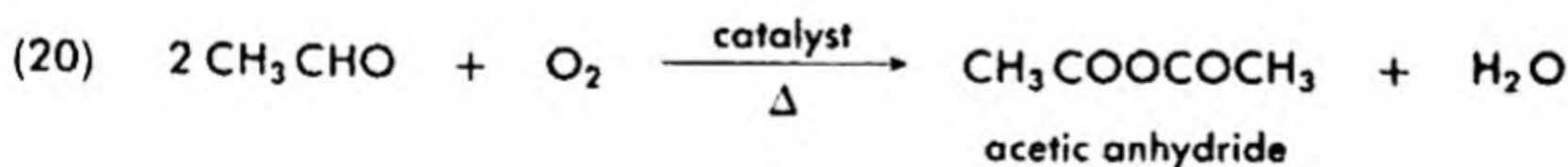


G. Air Oxidation of Aldehydes

Uncatalyzed oxidation of aldehydes in air, called "autoxidation," is a free radical process and is discussed in §26-4C(2). This oxidation usually produces acids, although peroxy acids can sometimes be obtained by very rapid oxidation with gaseous oxygen.



Catalyzed air oxidation of hot acetaldehyde is used to prepare acetic anhydride industrially.



SUPPLEMENTARY READINGS

- Bailey, P. S., "The Reactions of Ozone with Organic Compounds," *Chem. Rev.* **58**, 925-1010 (1958).
 McNesby, J. R., and C. A. Heller, Jr., "Oxidation of Liquid Aldehydes by Molecular Oxygen," *Chem. Rev.* **54**, 325-346 (1954).

QUESTIONS AND PROBLEMS

1. Write the equation for the preparation of phthalic anhydride from naphthalene.

2. Reduction of the ozonide of an alkene gave 1 mole of formaldehyde, 1 mole of acetone, and 1 mole of glyoxal. Write the structural formula of the alkene and show how the products were obtained from it.

3. Reduction of the ozonide of an alkadiene gave 2 moles of acetaldehyde and 1 mole of pyruvaldehyde. Write the structural formula of the alkadiene and show how the products were obtained from it.

4. An unsaturated compound was ozonized and hydrolyzed in the presence of hydrogen peroxide. The products were monochloroacetic acid and cyclohexanone. Write the structural formula of the original compound and show how the products were obtained from it.

5. A hydrocarbon, C_8H_8 , was treated with ozone, then dilute hydrogen peroxide. The sole product was oxalic acid. Write the structural formula of the hydrocarbon.

6. Ozonolysis of C_6H_{10} gave 1 mole of acetic acid and 1 mole of isobutyric acid. Write the structural formula of the hydrocarbon.

7. Show how a sample of pure pyruvaldehyde can be prepared from the suitable aromatic hydrocarbon.

8. Why can the position of the double bond in an olefin not be readily ascertained by addition reactions which do not cleave the molecule?

9. Show how the structures of the isomeric butenes can be established.

10. Complete combustion of a pure hydrocarbon gas occupying 19.04 ml. in 80.94 ml. of pure oxygen gave 61.90 ml. of product gases, of which 4.78 ml. remained after the mixture was shaken with sodium hydroxide solution. All gas measurements were made at the same temperature and pressure. Vapor pressure above the alkali solution was negligible. What was the empirical formula of the hydrocarbon?

11. Complete combustion of 21.52 ml. of a gas mixture containing methane, ethylene, and carbon monoxide with 78.38 ml. of pure oxygen gave 67.13 ml. of product gases, of which 36.17 ml. remained after the mixture was shaken with sodium hydroxide solution. All gas measurements were made at the same temperature and pressure. What was the volume analysis of the original gas mixture?

12. Ozonolysis of 2-pentene leads to the formation of a mixture of the ozonides of 2-butene, 2-pentene, and 3-hexene. Explain.

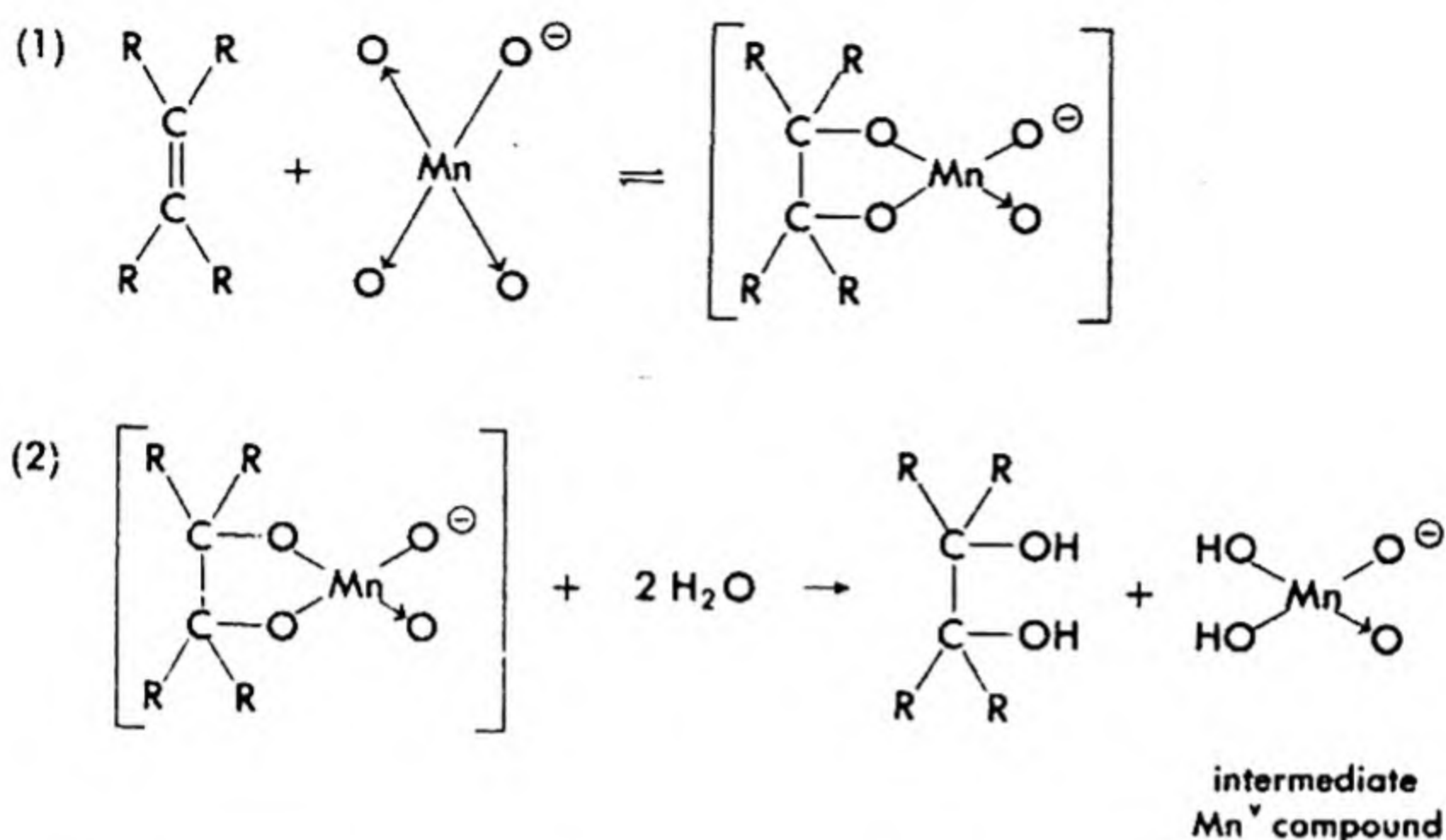
27-2 OXIDATION BY REAGENTS IN SOLUTION

The list of oxidizing agents which can be used to treat organic compounds in solution is almost endless. This section is limited to those solution oxidizing agents which are most useful and reactions of which are most general.

A. Oxidation of Alkenes

Potassium permanganate is not a highly selective oxidizing agent although it is a very useful one. The mechanism of the Baeyer test for unsaturation is representative of neutral permanganate oxidations. The

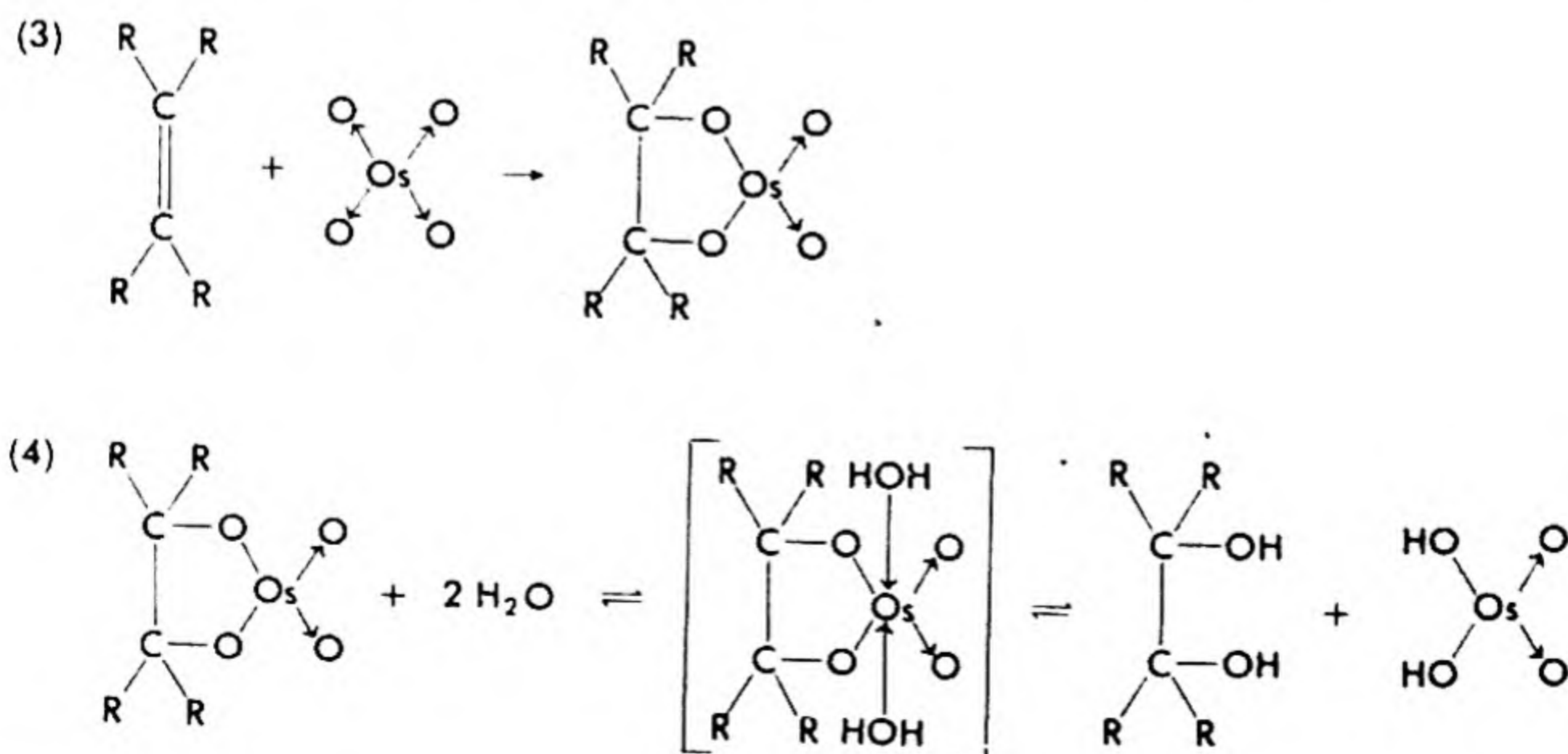
oxidation occurs *cis* at the double bond, suggesting a possible cyclic intermediate.



The intermediate Mn^V compound is believed to disproportionate to permanganate and manganese(IV) oxide.

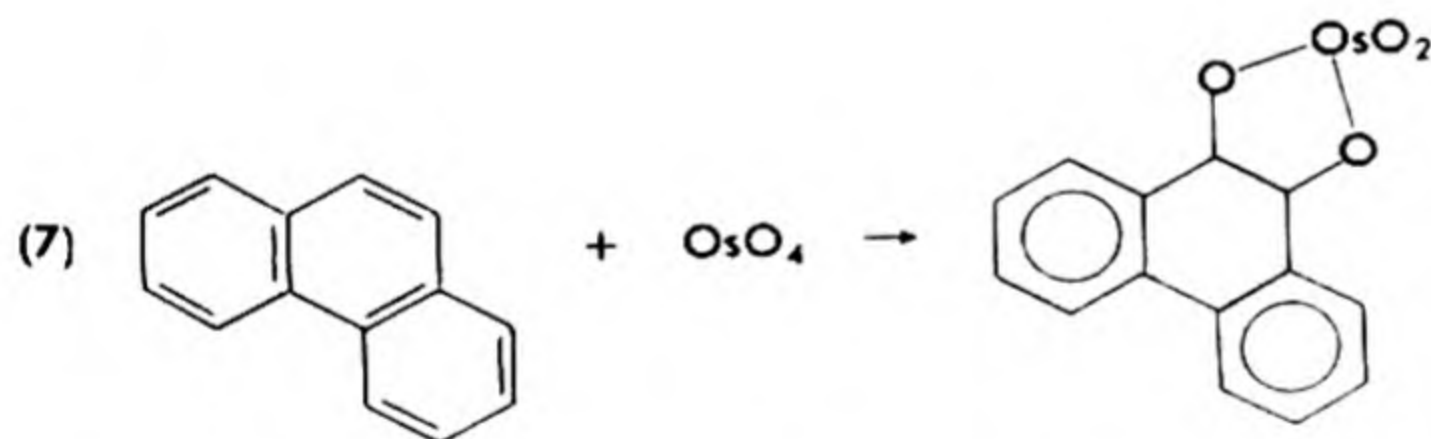
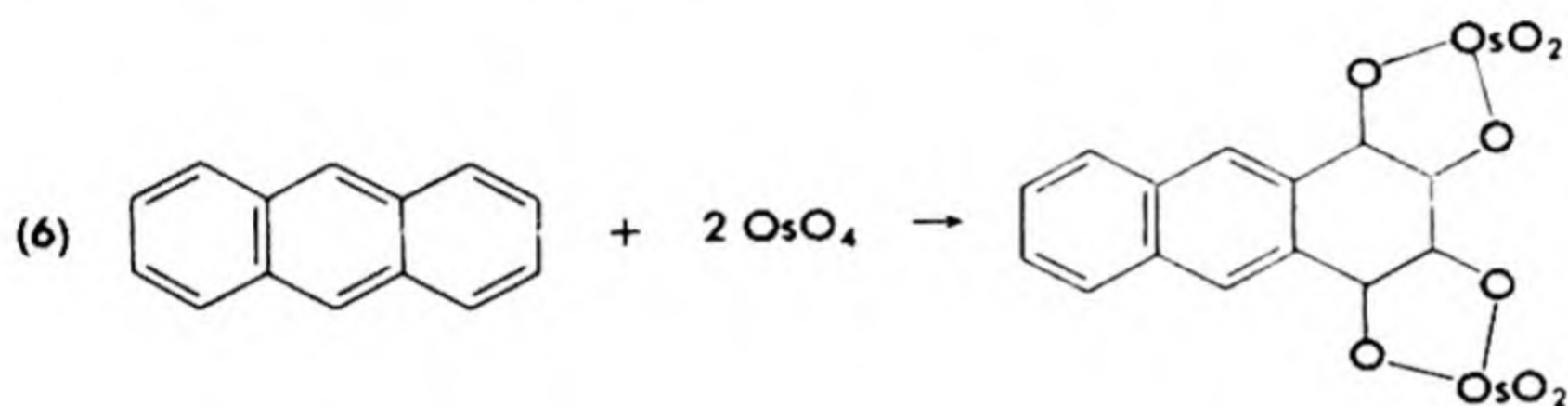
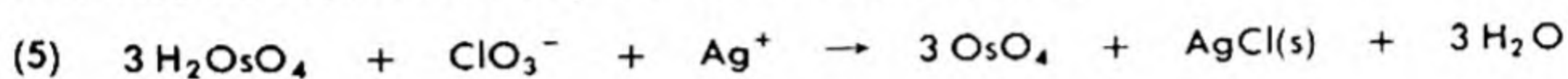
An oxidizing agent which produces glycols in better yield from olefins is osmium tetroxide. Unlike potassium permanganate, osmium tetroxide is capable of oxidizing some polynuclear aromatic hydrocarbons to dihydroxy derivatives (see eqs. 6 and 7).

Osmium tetroxide also readily oxidizes alcohols and amines, hence hydroxy and amino groups must be protected. The reagent is used in ether solution. An addition complex forms, which is decomposed by water to the glycol and osmic(VI) acid. Addition of pyridine during the complex formation speeds the reaction.



Like permanganate oxidation, osmium tetroxide oxidation occurs *cis* to the double bond.

Whereas potassium permanganate is nonvolatile, osmium tetroxide is quite volatile and very poisonous. It also has another disturbing property. Contact with the oxide or its vapors produces a very permanent black pigmentation over the skin, due to reduction of the oxide by the underlying layers of fat. This may cause blindness if the eye is affected. This is avoided by use of adequate forced ventilation and well trapped systems. A more serious hindrance to large scale use of osmium tetroxide is its high cost, about \$15 a gram. This requires very careful recovery of the osmic acid and its reoxidation by silver chlorate (eq. 5).



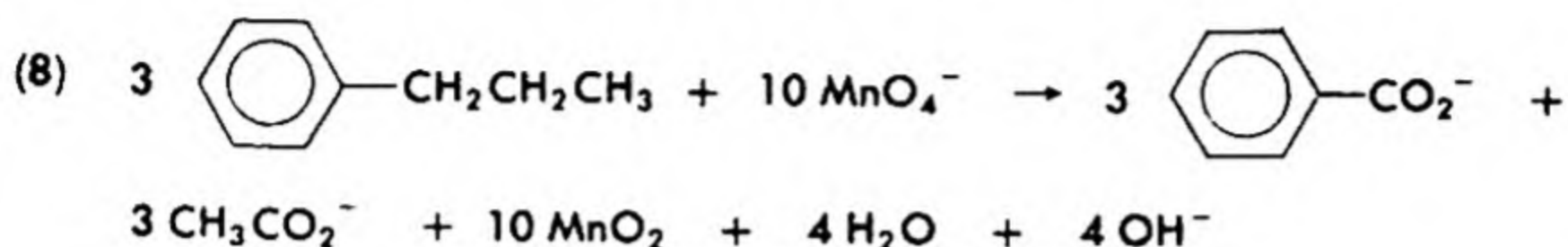
It is of interest that osmium tetroxide is the only oxidizing agent to attack the 1,2- and 3,4- positions of anthracene rather than 9,10- positions.

B. Oxidation of Aliphatic Side Chains on Aromatic Compounds

Aliphatic groups on aromatic rings are more readily oxidized than alkanes. The initial attack occurs at the carbon atom adjacent to the ring. Such an effect might be expected as a consequence of the unusually low bond dissociation energies for C—H bonds adjacent to the benzene ring. This is another way of saying that the aromatic ring stabilizes radical formation at the alpha position.

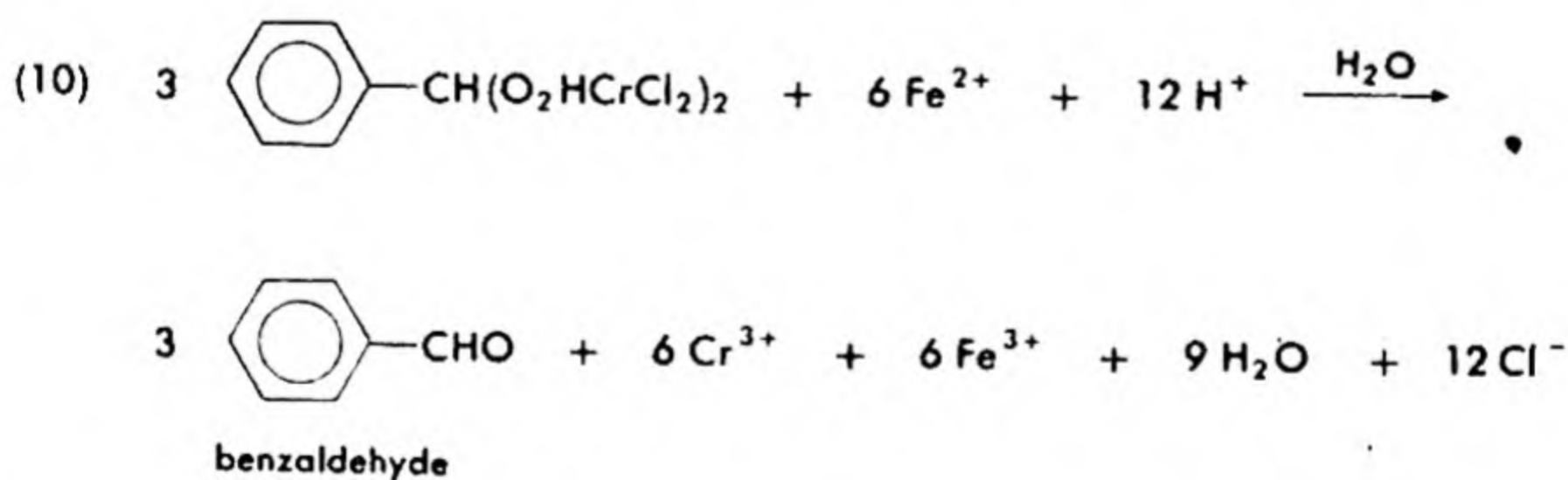
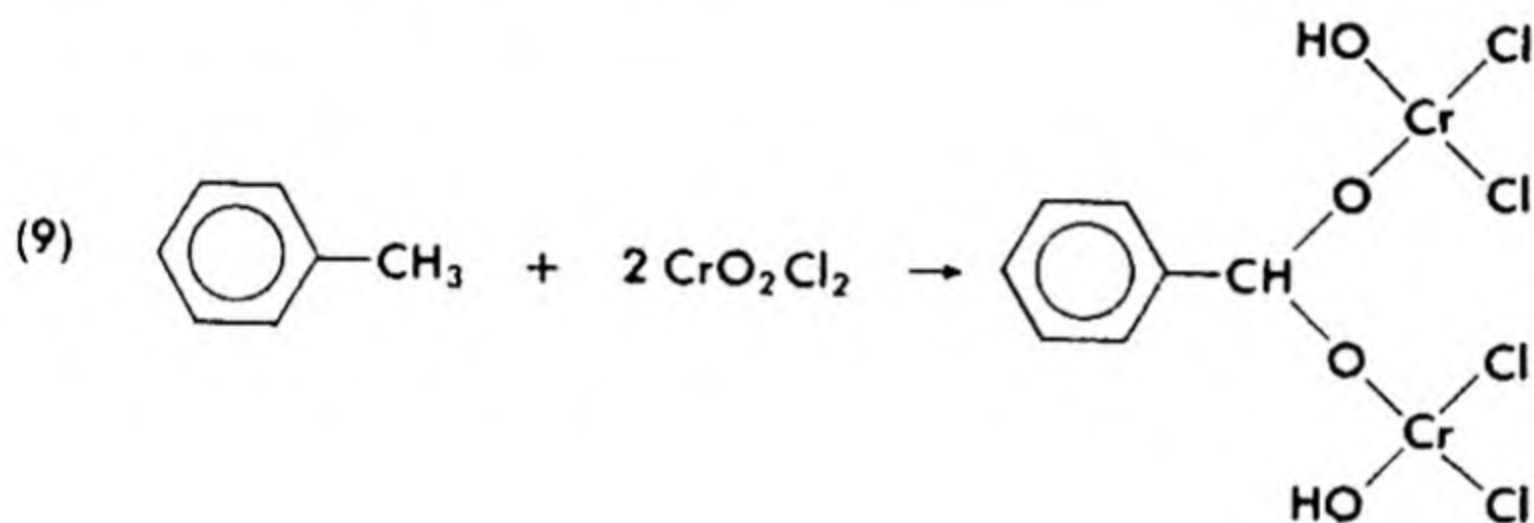
The oxidation probably occurs in stepwise fashion, by conversion of the hydrocarbon to an alcohol, then to an aldehyde or ketone, then finally to the carboxylic acid, with cleavage of any remaining portion of the side chain. However, conditions of the initial oxidation of the hydrocarbon

are so drastic, and the intermediate oxidation stages so much more easily oxidized further, that intermediate alcohols and carbonyl compounds are incapable of being isolated in more than trace amounts.



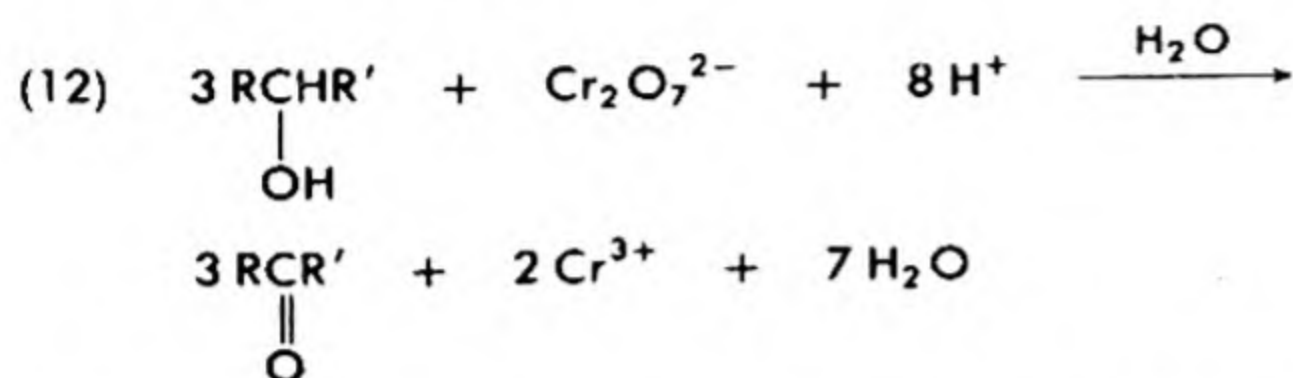
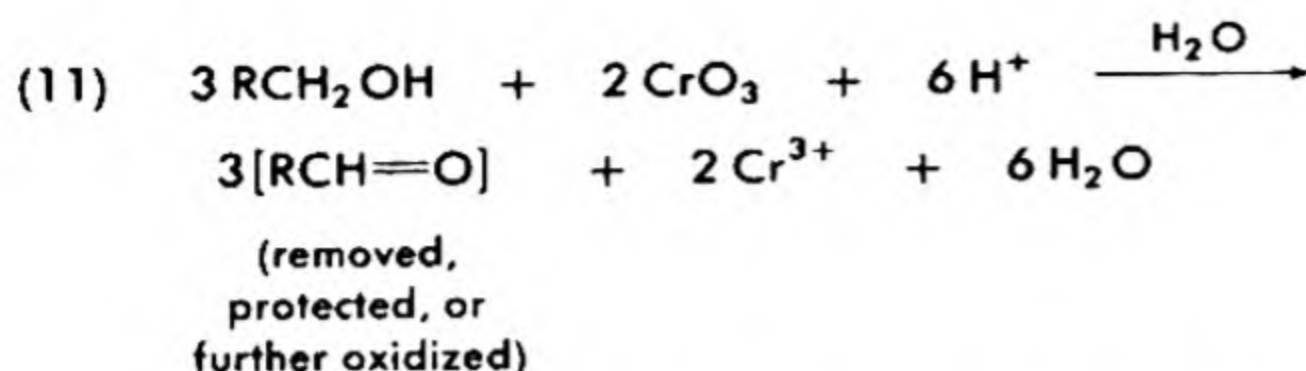
Side chain oxidations are accomplished by use of alkaline permanganate solutions, permanganate in glacial acetic acid, or dilute nitric acid.

A satisfactory way of oxidizing methylbenzenes to the corresponding aldehydes is the *Étard method* using chromyl chloride. Volatile, pyrogenic compounds such as chromyl chloride must be handled with extreme care both in regard to toxic vapors and in regard to avoidance of flammable mixtures. Use of chromyl chloride in carbon tetrachloride solutions diminishes danger of fires.

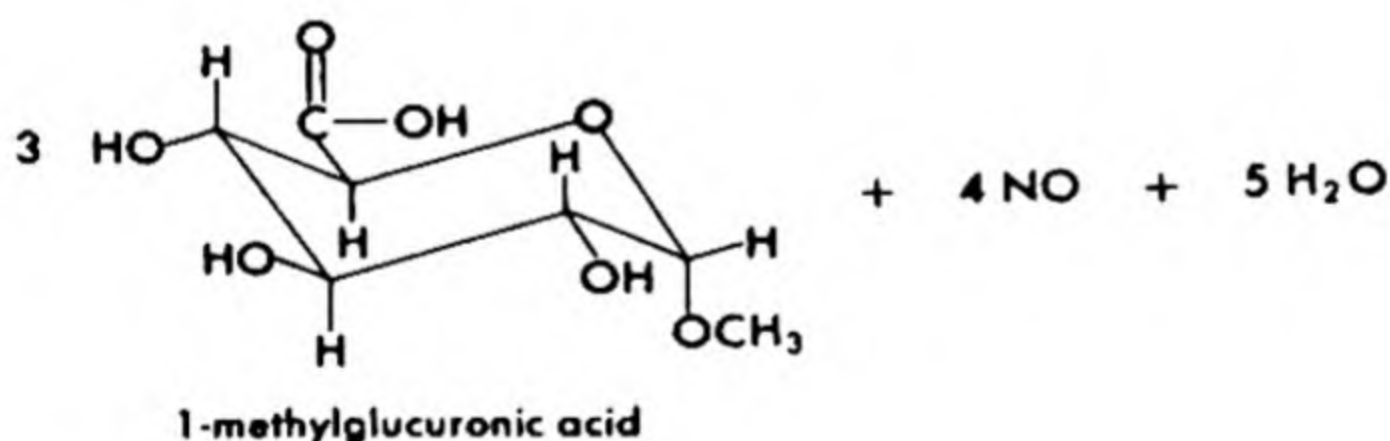
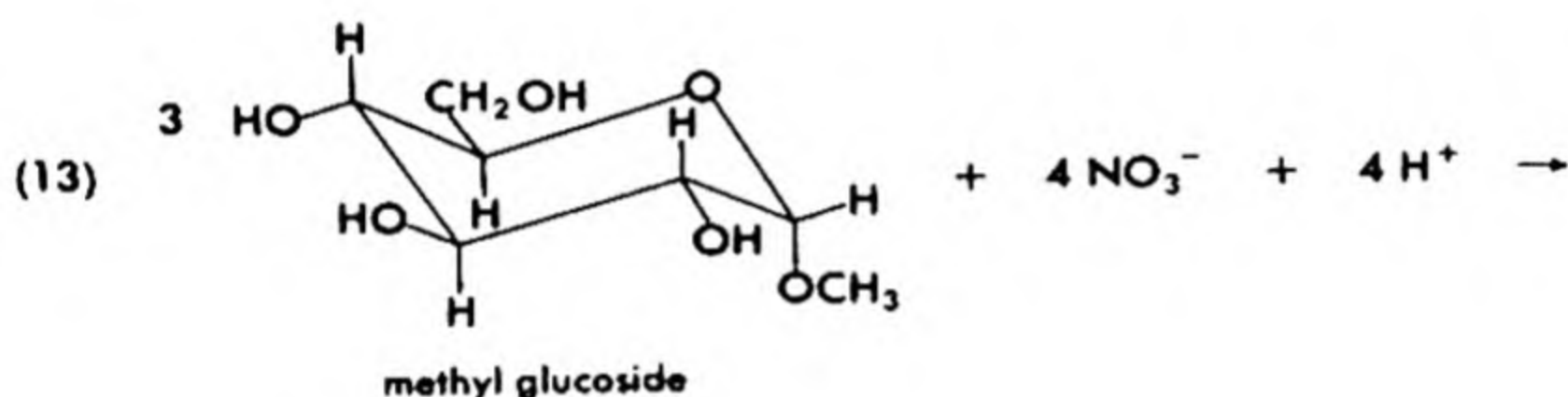


C. Oxidation of Primary and Secondary Alcohols

Alcohols with hydrogen on the carbinol carbon atom are readily oxidized by a number of reagents, such as permanganate, dichromate or chromium(VI) oxide, and dilute nitric acid. The immediate products are aldehydes from primary alcohols and ketones from secondary. However, since aldehydes are more readily oxidized than the parent alcohols, these are isolated as products only when special procedures are used to remove or protect them as fast as they are formed.

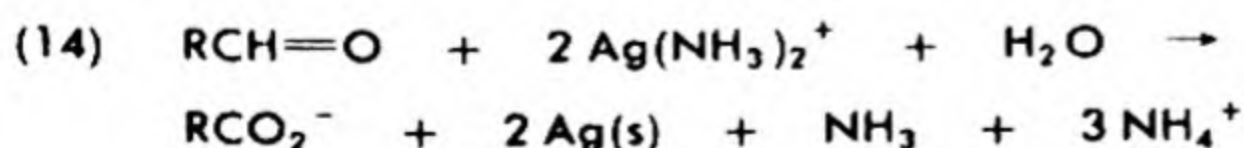


Dilute nitric acid is especially useful for oxidizing primary alcohol groups in the presence of secondary, which react more slowly. Fair yields of hydroxy acids are obtainable by this method, which has been applied extensively in sugar chemistry.



D. Oxidation of Aldehydes

The aldehyde group is very readily oxidized. *Tollens' reagent*, the silver diammine complex, attacks some aromatic amines, hydrazines, and a few



phenols as well as aldehydes. The silver coats the inside of the reaction vessel. This observation is used as a test for aldehydes. Mirrors are produced commercially in this way as well.

Moist silver oxide is a selective oxidizing agent of value in syntheses because of its ability to oxidize aldehyde groups in the presence of other oxidizable groups such as amino groups. Some groups, however, are attacked in other ways. Mercapto groups, for example, form silver mercaptides.

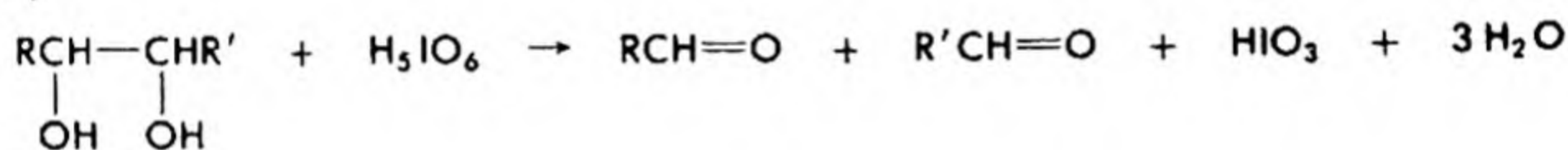
Bromine water is another fairly selective oxidizing agent. It oxidizes aldehyde groups to carboxyl groups without attacking either primary or secondary hydroxy groups on the same molecule.

E. Oxidation of Vicinal Glycols and Related Compounds

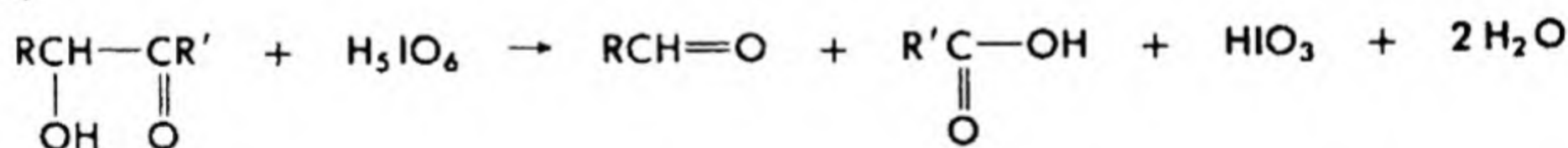
Two procedures are available for the selective oxidation of vicinal glycols and some of their more highly oxidized derivatives.

The *Malaprade reaction* is especially suitable for vicinal glycols and hydroxyketones that are soluble in water, but can be used also with water-insoluble compounds by a slight modification of the procedure. The method consists of treatment of the compound to be oxidized with aqueous periodic acid or, in the case of water-insoluble compounds, periodic acid in dioxane. Typical results are illustrated in eqs. (15) through (17).

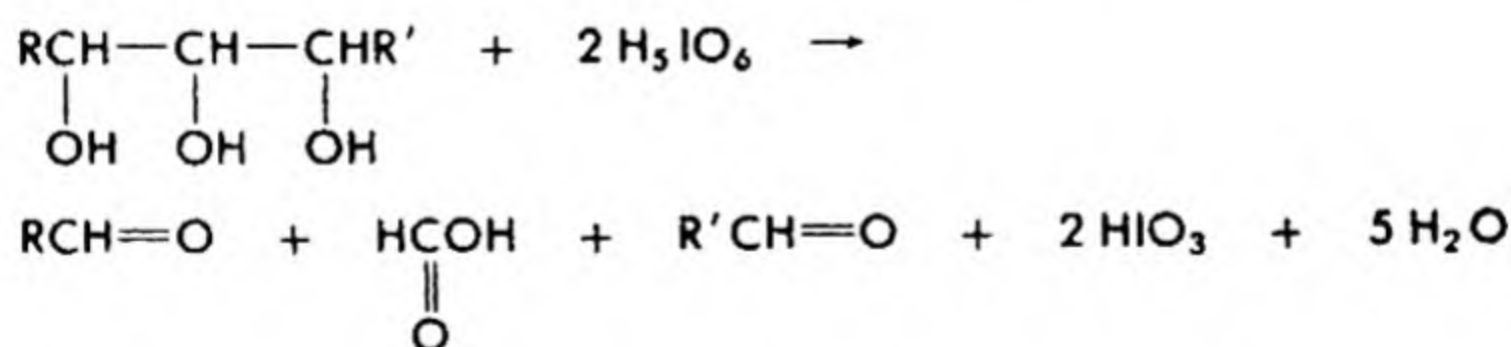
(15)



(16)



(17)

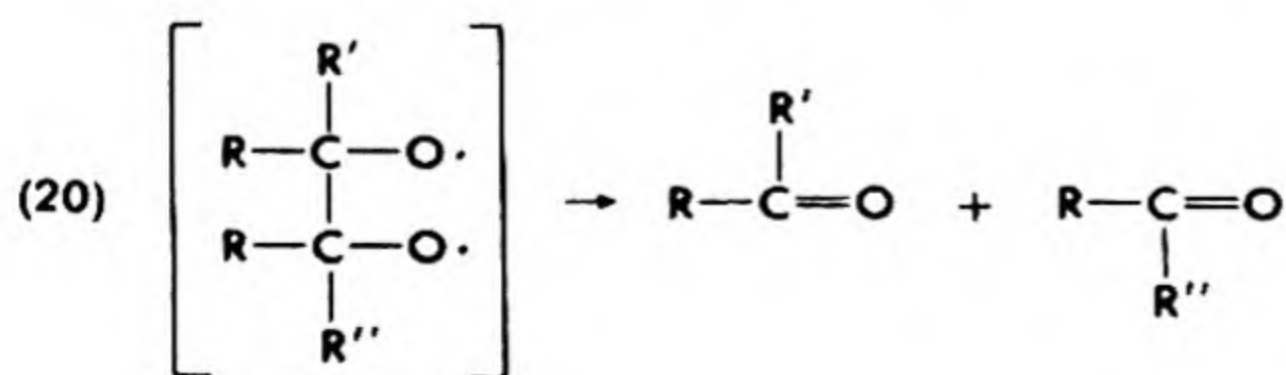
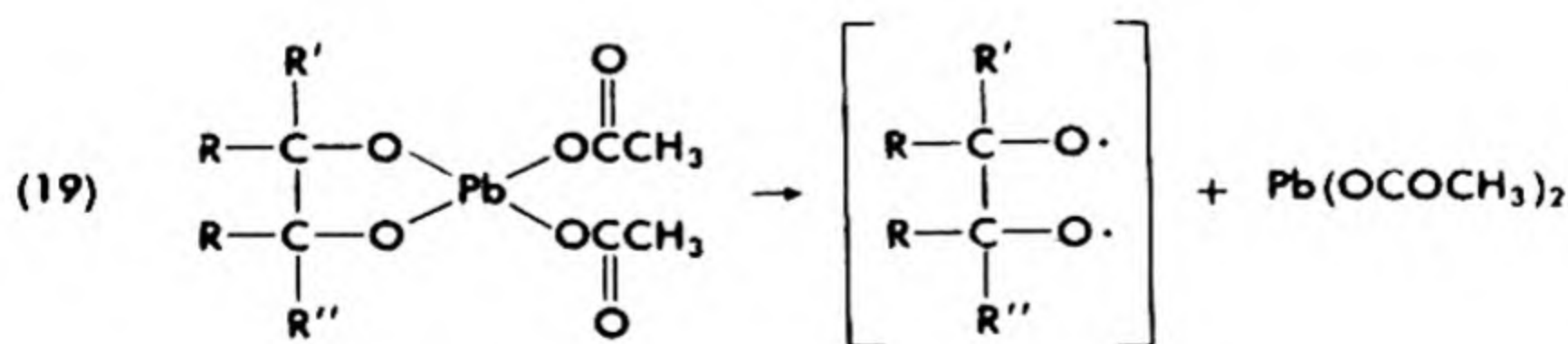
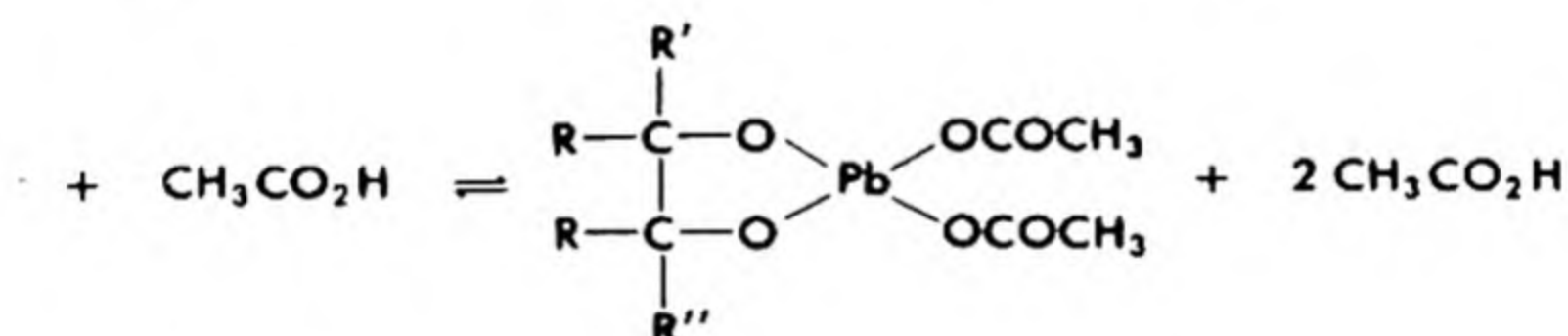
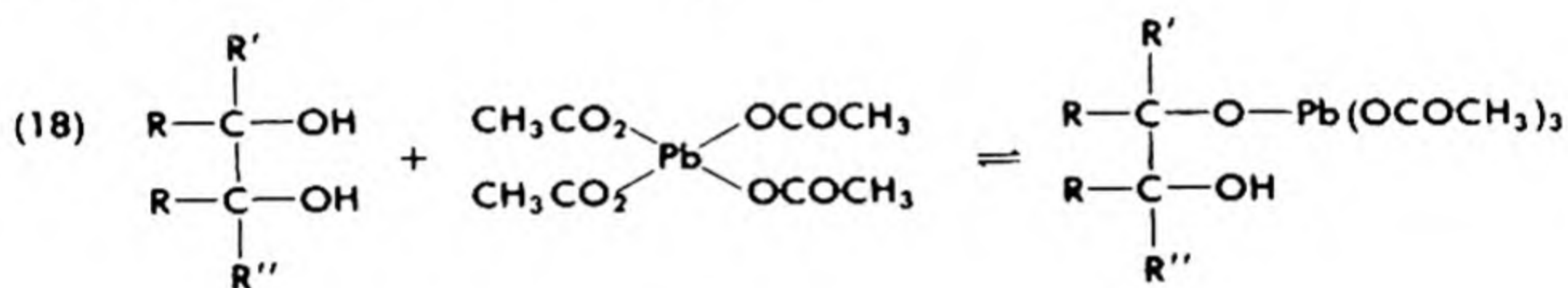


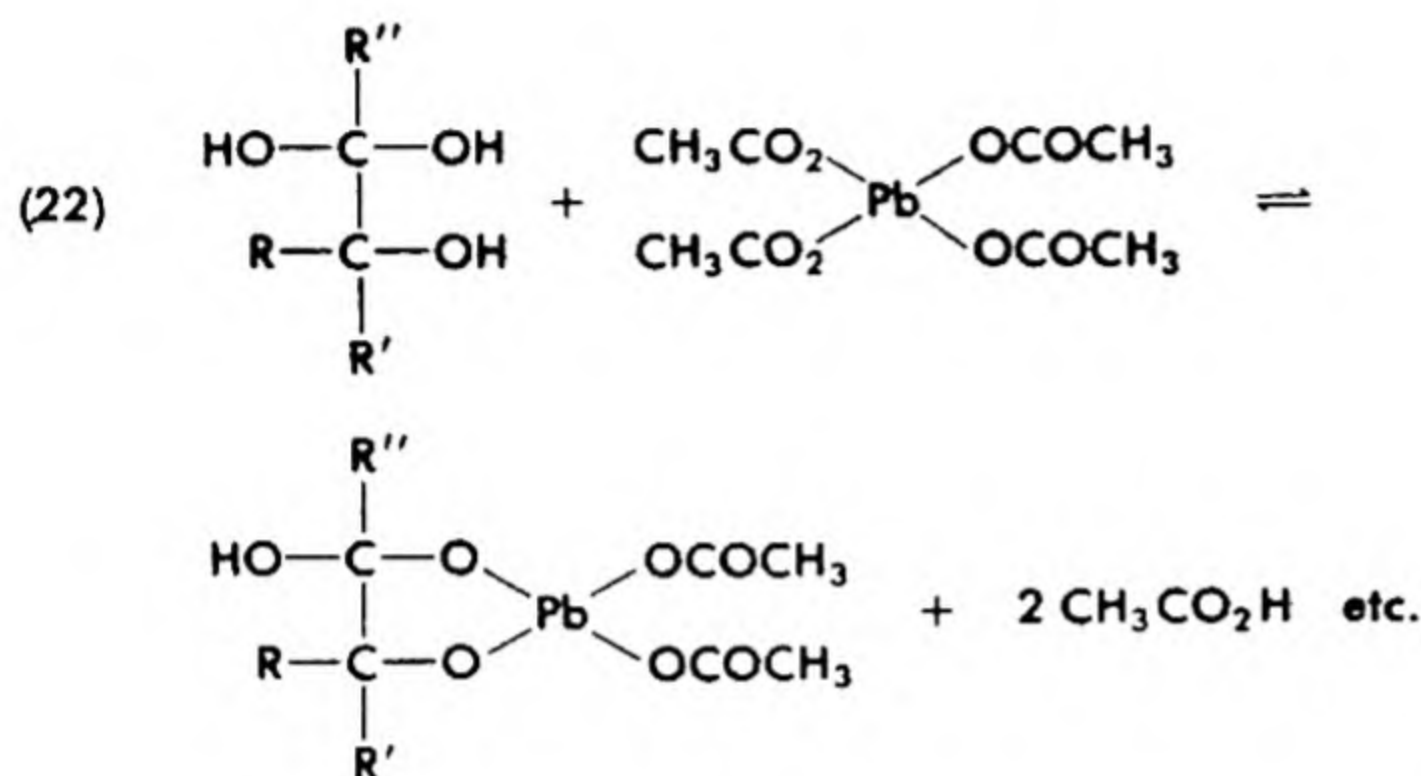
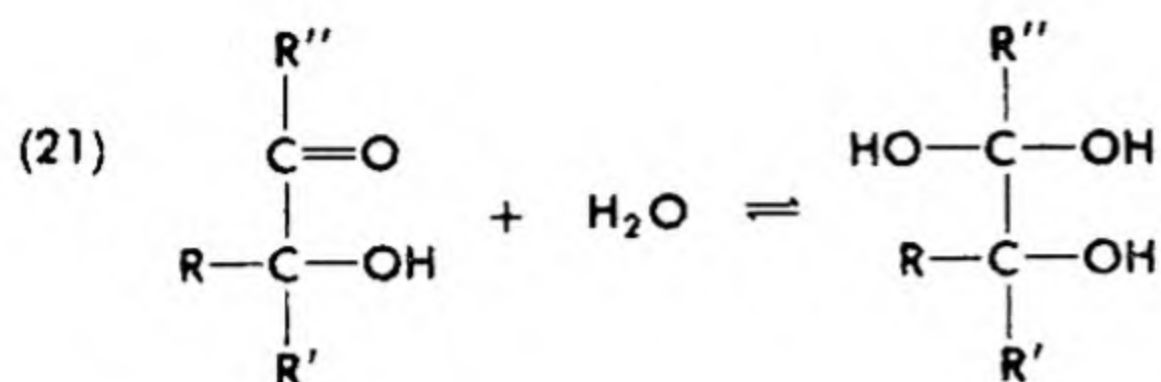
Simple aldehydes, alcohols, and polyoxygenated compounds with the groups farther apart than adjacent carbon atoms do not react with the reagent under the usual conditions of the reaction. *Alpha*-hydroxy acids likewise fail to react.

The second procedure, applicable especially to water-insoluble vicinal glycols, is the *Criegee reaction*. This consists of treatment of the glycol or its derivative with lead tetraacetate in cold glacial acetic acid solution. The reagent oxidizes all of the compounds attacked by periodic acid as well as *alpha*-hydroxyacids.

(1) *Mechanisms of Oxidation.* The mechanism of periodate oxidation is not yet established. Some chemists believe a cyclic intermediate is involved, as is the case with lead tetraacetate. However, evidence for such a mechanism is tenuous.

The main evidence for a cyclic intermediate in the Criegee reaction is the considerable difference in reaction rates of lead tetraacetate with *cis*- and *trans*-1,2-cyclopentanediols and with open chain glycols. *cis*-Glycols, which can form a cyclic intermediate most readily, react fastest. *trans*-Glycols, in which the hydroxy groups are restrained in positions unfavorable to cyclic intermediate formation, react slowest. Open chain glycols, not restrained to either configuration, react at intermediate rates. Similar, but less conclusive evidence based on 1,2-cyclohexanediols has been used to support a cyclic mechanism for periodate oxidation. Chair cyclohexane can form either *cis* or *trans* cyclic derivatives with nearly equal ease; the difference in oxidizability of the diols may well be due to other mechanistic factors than stereochemistry.





Although both periodic acid and lead tetraacetate undergo many other reactions as oxidizing agents at higher temperatures, the reactions described in this section are quantitative as long as the temperature is in the neighborhood of 20–25°. Other structural features known to be oxidized by these reagents in this range of temperature are the related vicinal amino alcohols and amino ketones.

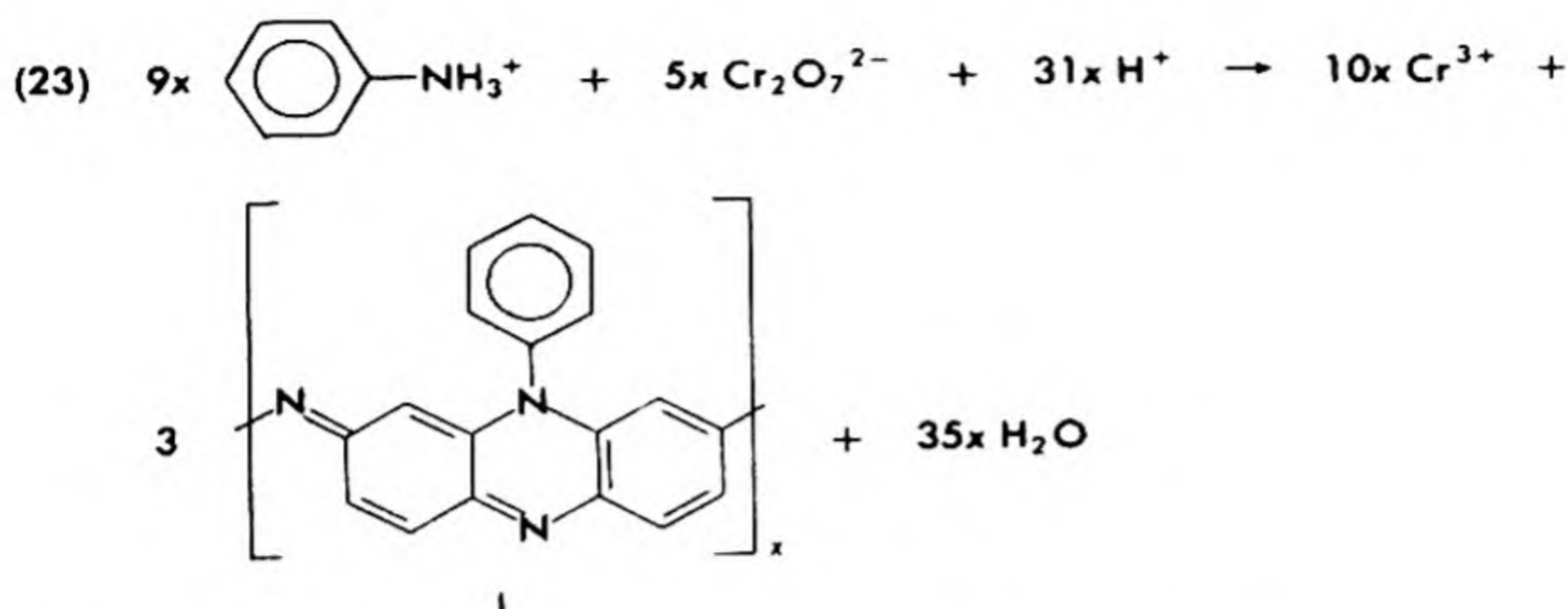
F. Oxidation of Aromatic Nuclei to Quinones

Chromic acid oxidation of certain aromatic systems gives quinones. The ease of quinone formation from aromatic compounds is *p*-dihydroxyarenes > *o*-dihydroxyarenes > aminoarenes > hydroxyarenes > arenes. Only those rings in which aromaticity is low, such as the middle rings of anthracene and phenanthrene, are readily oxidized to quinones without hydroxy or amino groups to activate the ring toward oxidation.

ortho-Quinones are very unstable and must be prepared in nonaqueous media (one notable exception is 9,10-phenanthrenequinone).

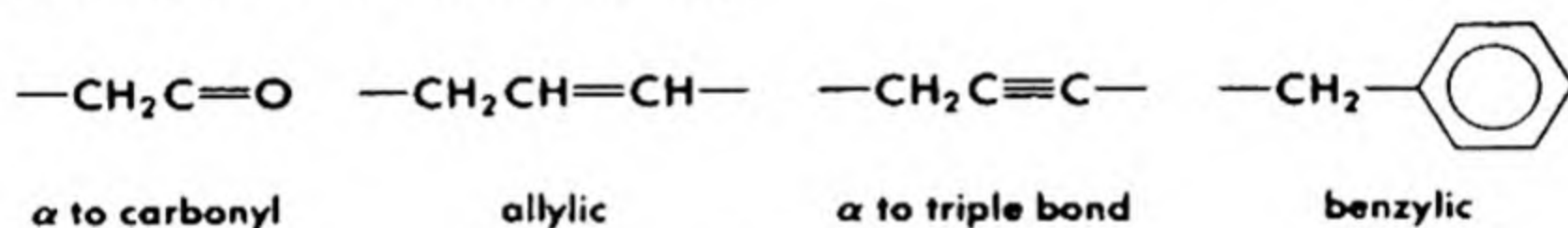
When free radicals are intermediates, that is, when one-electron oxidizing agents are involved, extensive side reactions involving coupling of radicals and attack upon solvents may ensue. For example, oxidation of a α -naphthol with potassium ferricyanide gives 4,4-dihydroxy-1,1'-binaphthyl as the main product. Arylamines undergo condensations with the partly oxidized or fully oxidized products. One such reaction which has practical importance is the manufacture of the dye, aniline black, by incomplete quinonoid oxidation of aniline. The dye is prepared directly

on the fabric and consists of a mixture of complex polymeric materials such as I.

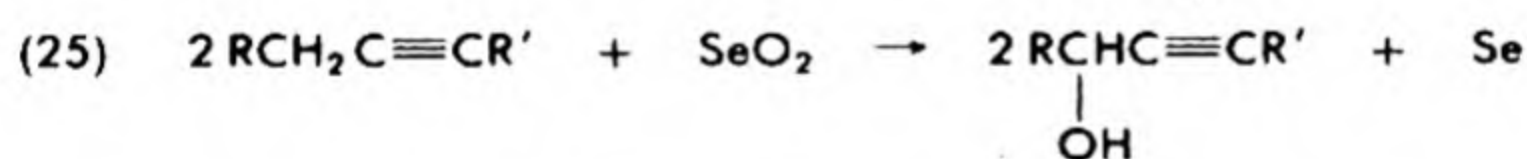
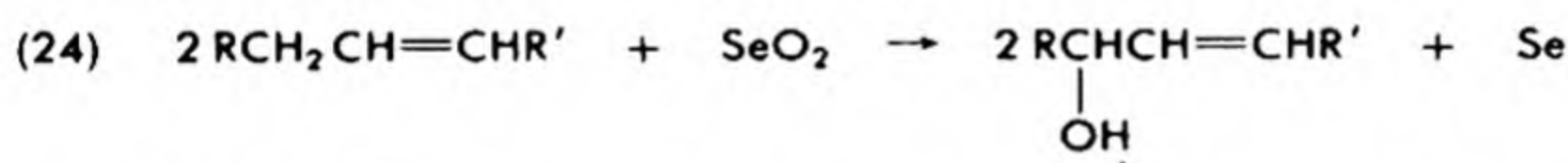


G. Selenium Dioxide Oxidation of Active Methylene Groups

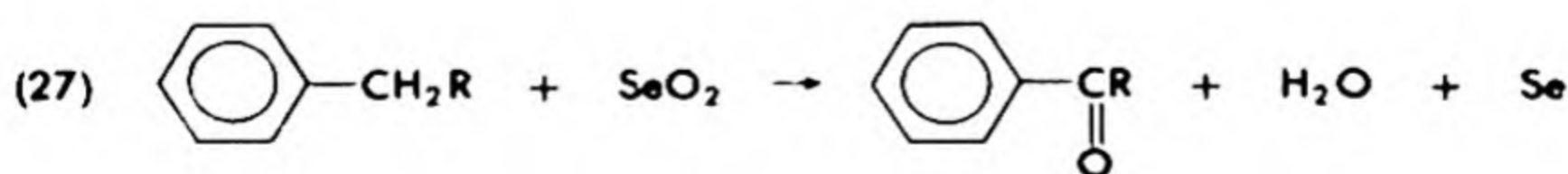
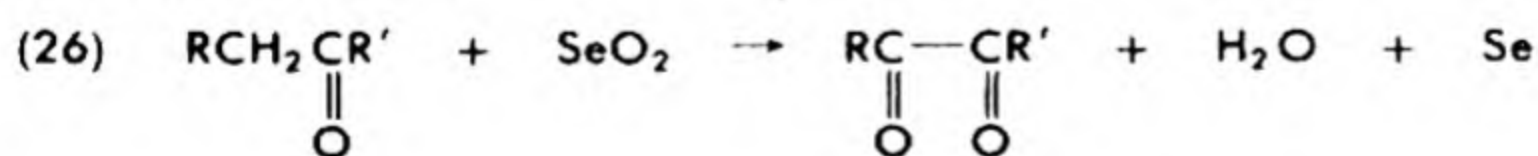
Selenium dioxide selectively attacks the methylene groups having structural features such as the following.



Alkenes and alkynes are generally oxidized to alcohols.



Other active methylene compounds are generally oxidized to carbonyl compounds. Aldehyde groups, however, may be further oxidized to carboxyl groups.

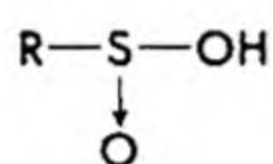


H. Oxidation of Sulfur Compounds

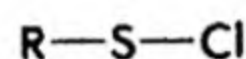
Mercaptans and thiophenols are highly sensitive to mild oxidation at the S—H bond. Very mild oxidizing agents, such as iodine, ferric ions,

dilute hydrogen peroxide, and *N*-chlorosuccinimide, give excellent yields of disulfides from mercaptans, thiophenols, and thioacids.

Stronger oxidizing agents, such as 30% hydrogen peroxide, potassium permanganate, and concentrated nitric acid, oxidize sulfur atoms stepwise to their highest valence states possible without removal of hydrocarbon groups. Oxidation of sulfides gives first sulfoxides, then sulfones. Disulfides can be oxidized to sulfinic acids. Sulfonic acids and sulfonyl chlorides are readily obtained. The latter are produced by oxidation of disulfides with chlorine and nitric acid. The chlorine atom doubtless adds to the sulfur atom first, since the halogen alone gives sulfenyl chlorides.

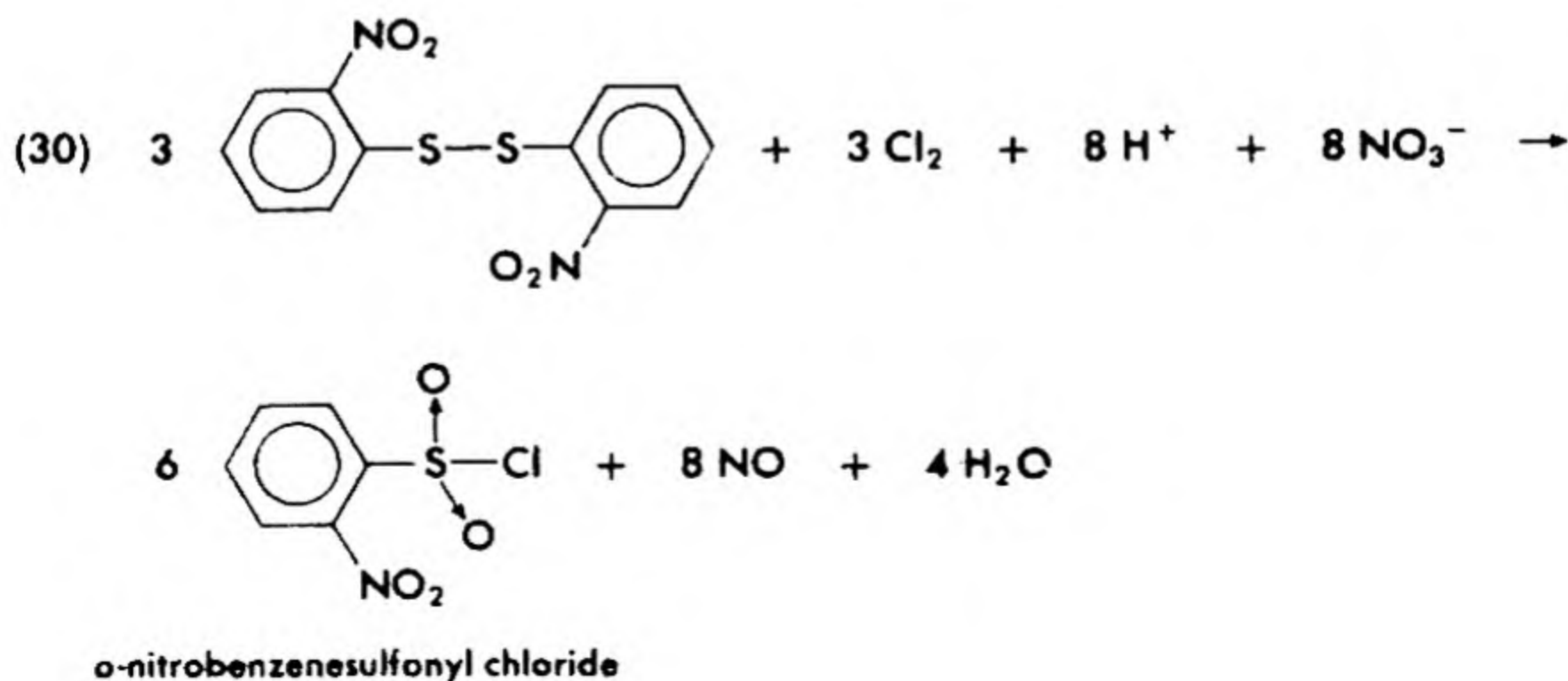
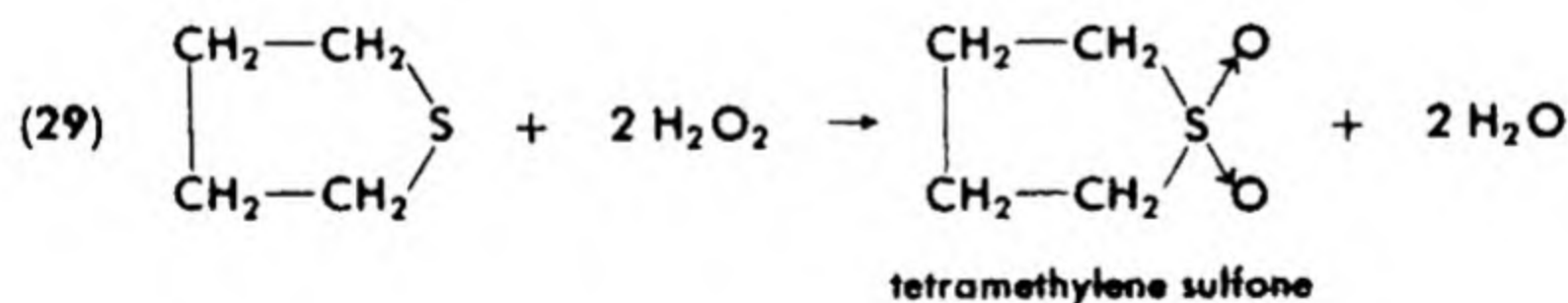
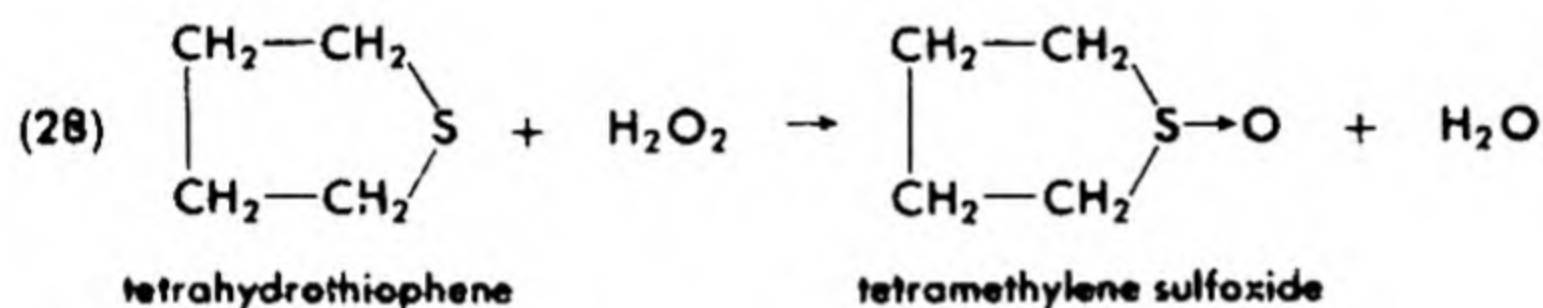


a sulfinic acid



a sulfenyl chloride

Some examples are the preparation of tetramethylene sulfoxide in 90% yield, tetramethylene sulfone in 97% yield, and *o*-nitrobenzenesulfonyl chloride in 84% yield by the reactions indicated in the equations below.



SUPPLEMENTARY READINGS

- Cason, J., "Synthesis of Benzoquinones by Oxidation," *Org. Reactions* **4**, 305-361 (1948).
- Gunstone, F. D., "Hydroxylation Methods," *Adv. Org. Chem.*, **1**, 103-147 (1960).
- House, H. O., *Modern Synthetic Methods*, Benjamin, New York, 1965, pp. 78-104.
- Jackson, E. L., "Periodic Acid Oxidation," *Org. Reactions* **2**, 341-375 (1944).
- Ladbury, J. W., and C. F. Cullis, "Kinetics and Mechanism of Oxidation by Permanganate," *Chem. Rev.*, **58**, 404-410, 425-432 (1958).
- Rabjohn, N., "Selenium Dioxide Oxidation," *Org. Reactions* **5**, 331-386 (1949).
- Stewart, R., "Oxidation Mechanisms—Applications to Organic Chemistry," Benjamin, New York, 1964.
- Waters, W. A., *Mechanisms of Oxidation of Organic Compounds*, Methuen, London, Wiley, New York, 1964.
- Waters, W. A., "Oxidation Processes," in H. Gilman, *Organic Chemistry. An Advanced Treatise*, Vol. IV, Wiley, New York, 1953, pp. 1120-1131 and 1180-1238.

QUESTIONS AND PROBLEMS

1. Write equations for the reactions that occur among the reagent mixtures given below. Use structural formulas for organic compounds. Indicate essential conditions.

- | | |
|---|---|
| a. stilbene + osmium tetroxide | h. acetophenone + selenium dioxide |
| b. <i>p</i> -xylene + aqueous potassium permanganate | i. diphenylmethane + selenium dioxide |
| c. glycerol + periodic acid | j. 1-bromo-2-butene + selenium dioxide |
| d. benzoin + lead tetraacetate + moist acetic acid | k. dimethyl sulfide + hydrogen peroxide, 1 mole |
| e. propylene glycol + dilute nitric acid | l. methyl isobutyl sulfide + hydrogen peroxide, 2 moles |
| f. phenanthrene + sodium dichromate + glacial acetic acid | m. thiophenol + iodine |
| g. 1,4-naphthalenediol + chromic acid + glacial acetic acid | |

2. Show how the following compounds can be prepared in good yield from the suggested starting materials and inorganic compounds and elements. Use structural formulas for organic compounds. Indicate essential conditions and reagents.

- | | |
|--|--|
| a. 9,10-dihydroxy-9,10-dihydro-phenanthrene from phenanthrene | hydrin) from hydrindene |
| b. 1,2,3,4-tetrahydro-1,2,3,4-naphthalenetetrol from naphthalene | d. benzoquinone from benzene |
| c. triketohydrindene hydrate (nin- | e. pyruvic acid from lactic acid |
| | f. di(2-methylbutyl) isophthalate from <i>m</i> -xylene and 2-butene |
| | g. 4-hydroxy-3-methyl-2-butenic acid from acetone |

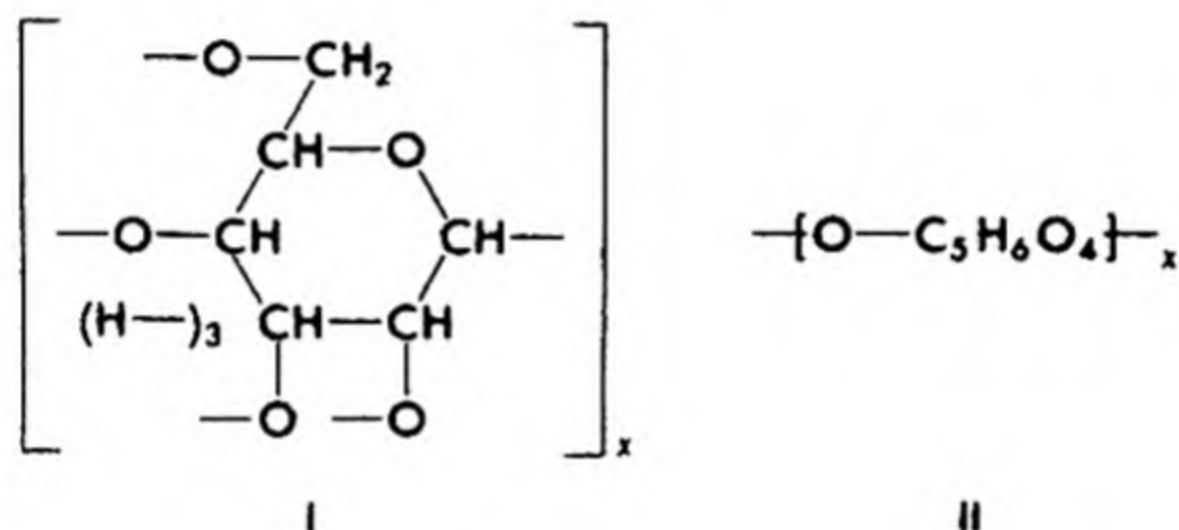
3. The following data were obtained by treatment of the unknown compounds described with periodic acid or lead tetraacetate. Reconstruct as much of the structure of each unknown compound as possible from the data given.

a. A cyclic trihydroxy compound, $\text{CH}_3\text{—C}_6\text{H}_{10}\text{O—C}_3\text{H}_7\text{O}_2$, treated with periodic acid gave formaldehyde and a ketone, $\text{CH}_3\text{—C}_6\text{H}_{10}\text{O—C}_2\text{H}_3\text{O}$.

b. A compound, $\text{C}_{10}\text{H}_{20}\text{O}_4$, treated with periodic acid gave 1 mole of formic acid, 1 mole of acetic acid, and 2-isopropylbutanedial. An isomer with the same carbon skeleton, treated with periodic acid gave 3-ketobutanal and 3-keto-4-methylpentanal.

c. A dicarboxylic acid, $\text{C}_8\text{H}_{14}\text{O}_6$, did not react with periodic acid, but was decarboxylated by lead tetraacetate in moist acetic acid to give a diketone, $\text{C}_6\text{H}_{10}\text{O}_2$. The same diketone was prepared in low yield by the action of zinc on chloroacetone.

d. A compound, I, gave a second compound, II, and x moles of formic acid upon periodic acid oxidation.



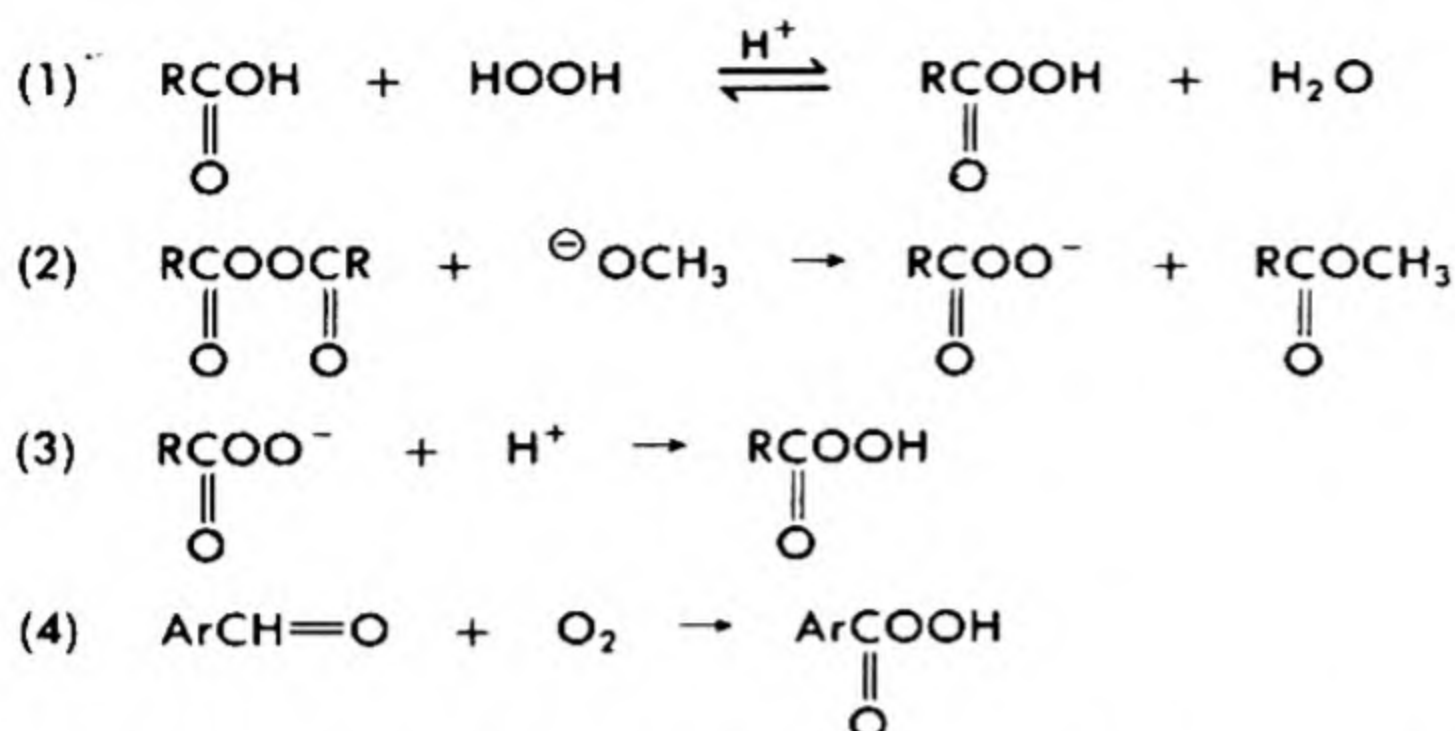
27-3 ORGANIC PEROXY COMPOUNDS

Recently, peroxides have achieved prominence in certain selective oxidations in the same way that metal hydrides have in reductions. Two main types of reactions are of interest, though many other types are known under different conditions. These are peroxidation and epoxidation-hydroxylation.

A. Peroxidation: Preparation of Organic Peroxides

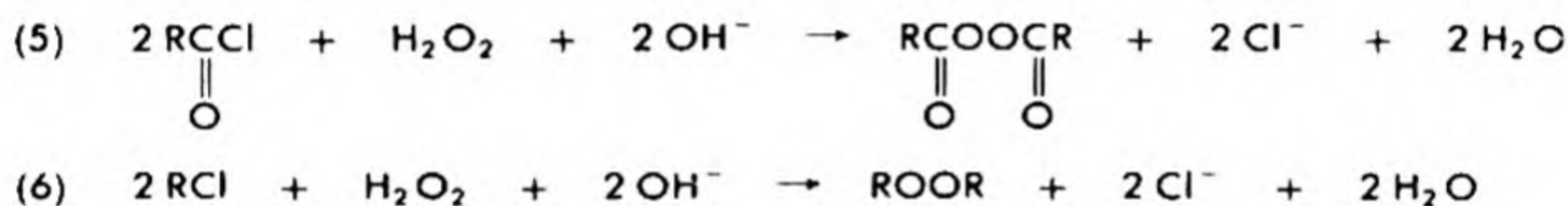
In view of what was written earlier about the instability and reactivity of organic peroxides (§7-3B and §27-1B), it may be surprising that peroxides are very easily formed. Several are stable enough to be isolated as crystalline solids. All, however, are capable of explosive decomposition under suitable conditions, hence must be treated with respect. Peroxides should never be recrystallized from hot solutions.

Three general methods are used for the preparation of organic peracids. Aliphatic peracids are prepared by treatment of the acids or their anhydrides with acidic hydrogen peroxide. Aromatic peracids are prepared by the same method, by hydrolysis of aroyl peroxides, and by rapid, light-promoted reaction of oxygen with an aromatic aldehyde.

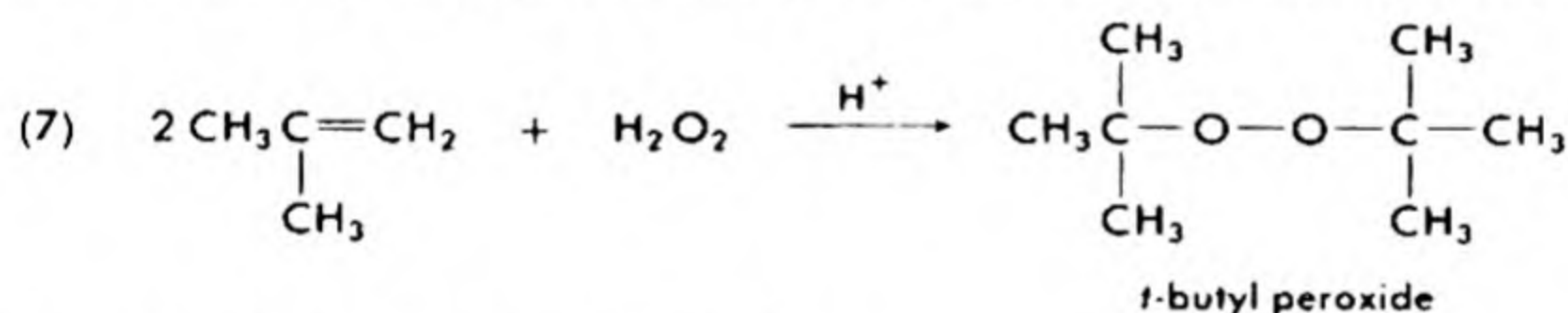


Perbenzoic acid can be prepared in 86% yield by the method indicated in eqs. (2) and (3). *m*-Chloroperbenzoic acid is now available commercially and is therefore a reagent of choice for laboratory epoxidations.

Acyl peroxides and alkyl peroxides are prepared by treating the respective halides with alkaline hydrogen peroxide solution (eqs. 5-6) or by

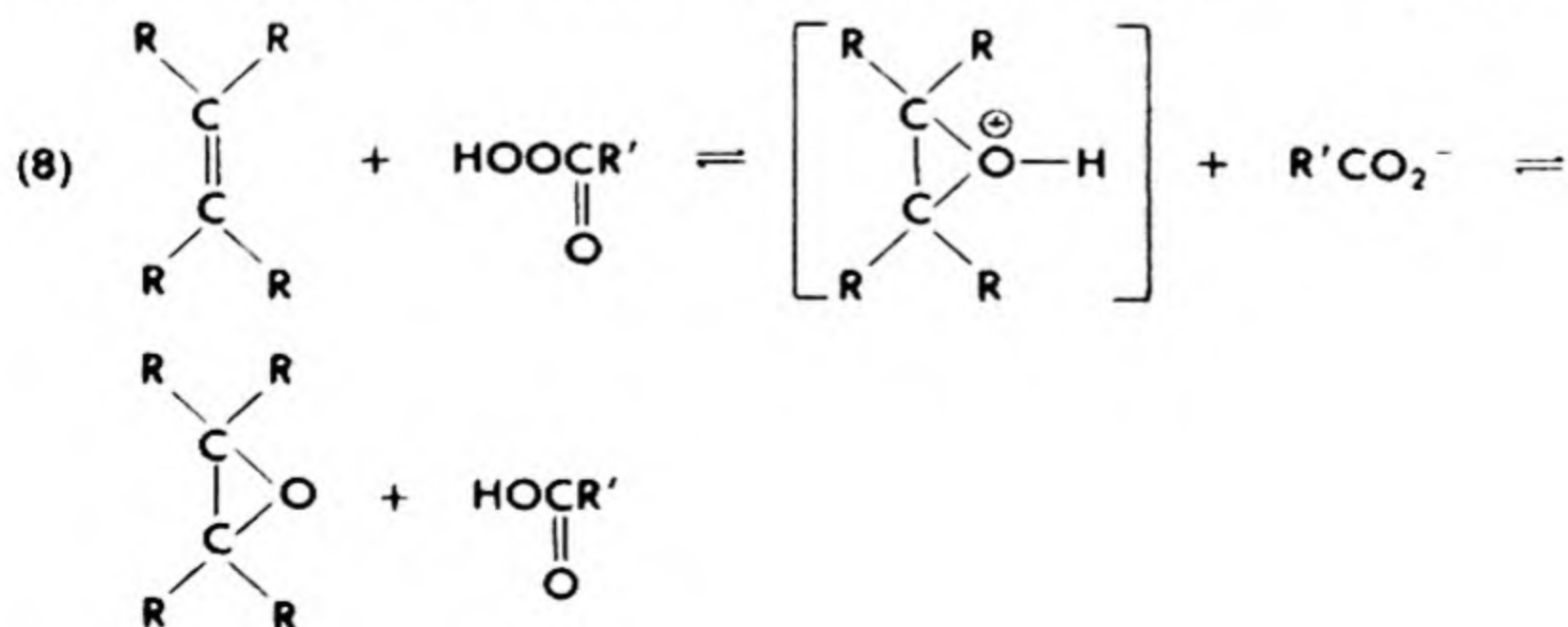


addition of hydrogen peroxide to olefins in acid solution (eq. 7).



B. Epoxidation and Hydroxylation

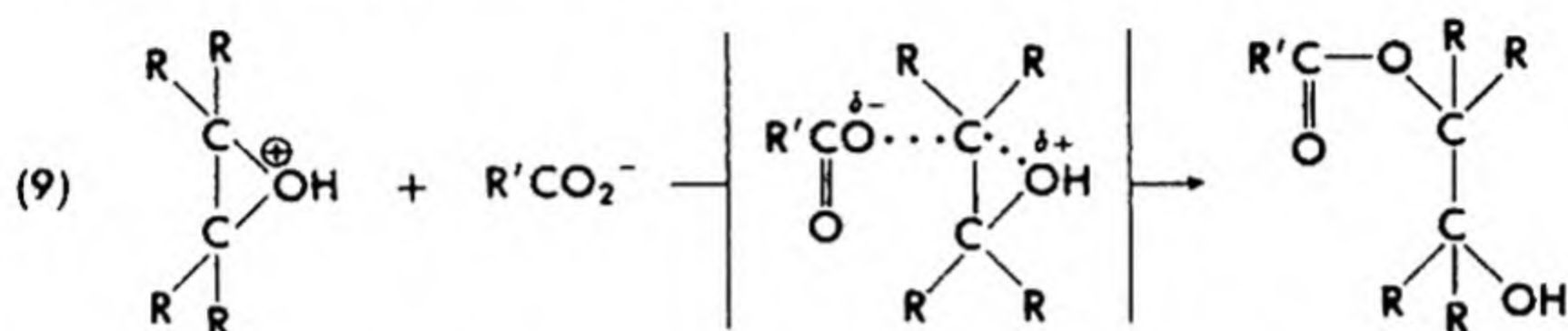
Oxidation of alkenes by peroxyacids selectively produces epoxides or glycol derivatives under the appropriate conditions. Epoxidation seems to be the first stage in either reaction; the formation of glycols and their derivatives, called hydroxylation, comes about as the result of ring-opening reactions. The reaction is thought to occur as in eq. (8).



When hydrogen peroxide is used, it is generally dissolved in glacial acetic acid. The actual reacting species in the mixture is peracetic acid (see eq. 1).

The addition mechanism proposed above agrees with the established fact that epoxidation occurs *cis* to the double bond.

Addition of water or the solvent acid to the epoxide usually occurs stereospecifically, resulting in inversion of configuration. This points to a direct displacement mechanism (eq. 9) (see §13-4A). Occasionally, the oxide opens via a carbonium ion process. In such a case other stereochemistry and/or rearrangements may be observed.



Epoxidation is effected best by treating the alkene with *m*-chloroperbenzoic acid in benzene or chloroform solution. The main product of treatment of an olefin with hydrogen peroxide in formic acid is the mono or diformate of the glycol. The glycol can be obtained from this by acid or alkaline hydrolysis.

SUPPLEMENTARY READINGS

- House, H. O., *Modern Synthetic Methods*, Benjamin, New York, 1965, pp. 105-133.
 Swern, D., "Epoxidation and Hydroxylation...", *Org. Reactions*, 7, 378-433 (1953).
 Waters, W. A., "Oxidation Processes," in H. Gilman, *Organic Chemistry, An Advanced Treatise*, Vol. IV, Wiley, New York, 1953, pp. 1153-1168.

PROBLEM

1. Write equations for the reactions that occur among the following mixtures of reagents. Use structural formulas for organic compounds. Indicate essential special conditions.

- | | |
|--|--|
| a. propylene + perbenzoic acid in chloroform | and hydrogen peroxide in glacial acetic acid (with trace of sulfuric acid) |
| b. cyclohexene + peracetic acid in benzene | f. benzoic acid and hydrogen peroxide (with trace of sulfuric acid) |
| c. styrene + perbenzoic acid in benzene | g. formic acid and hydrogen peroxide |
| d. <i>cis</i> -9-hexadecenoic acid, hydrogen peroxide, and formic acid | h. diphenylacetyl chloride and sodium peroxide |
| e. <i>cis</i> -2-butene-1,4-diol diacetate | |

REVIEW PROBLEM

1. Show how the following compounds can be prepared in good yield from the suggested starting materials and inorganic reagents. Use structural formulas for organic compounds. Indicate reagents and essential special conditions.

- a. 2-amino-2-methyl-3-phenylpropanoic acid from 1,4-diphenyl-2,3-dimethyl-2-butene and acetic acid
- b. 4-amino-6-methylnonane from 1-pentene and benzoic acid
- c. 1,1,1,5,5,5-hexaphenyl-2-methyl-3-pentyn-2-ol from 1,1,1-triphenylpropane
- d. 1,4-bis(2,5-dimethylphenyl)dichloromethyl benzene from *p*-xylene
- e. 4-methyl-3,5,6-triethyloctane-4,5-diol from 3-pentanone
- f. *cis*-1,2-cyclohexanediol from benzene
- g. *trans*-1,2-cyclohexanediol from phenol

28

Reduction

28-1 HYDROGENATION AND HYDROGENOLYSIS

Hydrogenation is the addition of hydrogen to an unsaturated linkage. Hydrogenolysis is the cleavage of a compound by means of hydrogen.

A. Conditions of Hydrogen Reactions

Molecular hydrogen is relatively stable and unreactive toward most organic compounds. It must be activated by use of a suitable catalyst.

Effective catalysts are those that adsorb and dissociate molecular hydrogen and at the same time adsorb and render more reactive the organic reagents. Generally used catalysts are nickel, palladium, platinum, ruthenium, and their oxides. The oxides may be reduced to the metals during the course of the reaction. Different behavior can sometimes be obtained with copper chromite or zinc chromite.

The crystal structure of the catalyst must meet exacting demands as the organic molecule must fit so as to form the maximum number of *weak* bonds with the catalyst, but no strong bonds.

High pressure increases not only the rate, but also the completeness of hydrogenation, since the products occupy less volume than the reagents.

Even with catalysts, elevated temperatures are often required to maintain practicable reaction rates.

B. Reaction Mechanisms

A complete discussion of hydrogenation and hydrogenolysis mechanisms entails the physics of solid surfaces and much detailed crystallography. Only a rather generalized, superficial treatment of the mechanism is possible here.

Several lines of evidence reveal the nature of hydrogenation phenomena:

1. *The reversibility of the reaction.* The equilibrium point can be varied by changing the hydrogen pressure so that either hydrogenation or dehydrogenation may occur.

2. *The sensitivity of the reaction to hydrogen pressure.* Not only the rate,

but even the kind of products formed may depend upon the pressure of hydrogen.

3. *The differing specificities of different catalysts.* Some catalysts favor saturation of one kind of linkage, some of other kinds of linkage.

4. *Stereospecificity of the reaction under mild conditions.* Hydrogen is added *cis* to a double or triple bond. Studies in complex molecules (steroids, Chapter 41) show that the hydrogen always approaches from the less hindered side, which is the side that must lie next to the catalyst surface.

The data suggest the following to be the steps of the catalytic hydrogenation process on metallic catalysts of the nickel group.

First, the hydrogen dissociates upon adsorption on the catalyst surface, and atomic hydrogen then enters the interstices between metal atoms in the crystal lattice. The metal can be shown to swell appreciably when hydrogen is adsorbed under pressure.

Next, the organic molecule is adsorbed, forming weak linkages with the metal that render more active the primary valences in the molecule. A kind of metallic π complex is formed. It is at this juncture that geometry is an important consideration (see Fig. 28-1). While the organic molecule

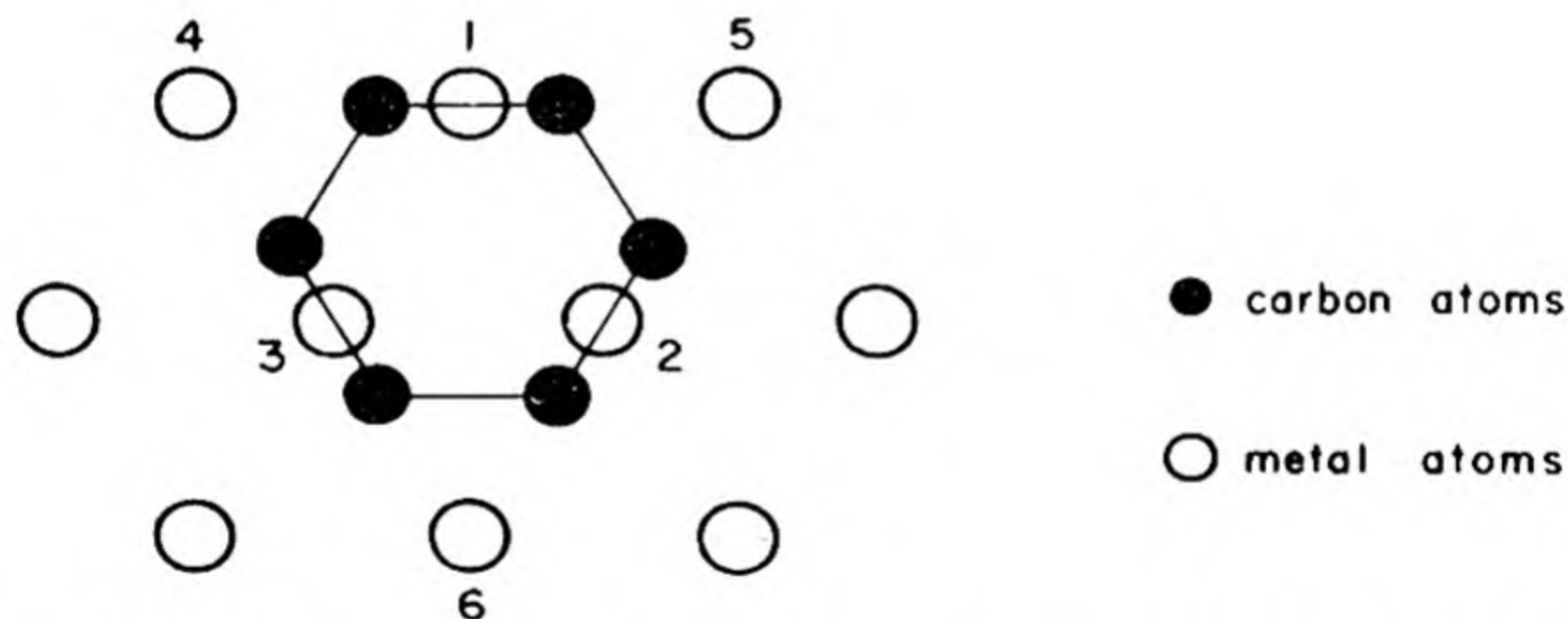
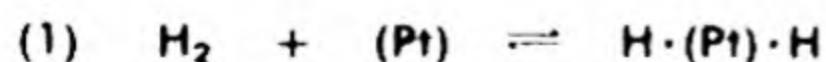
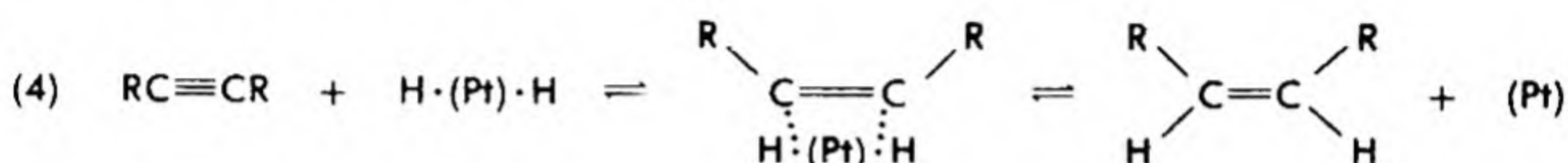
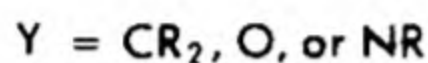
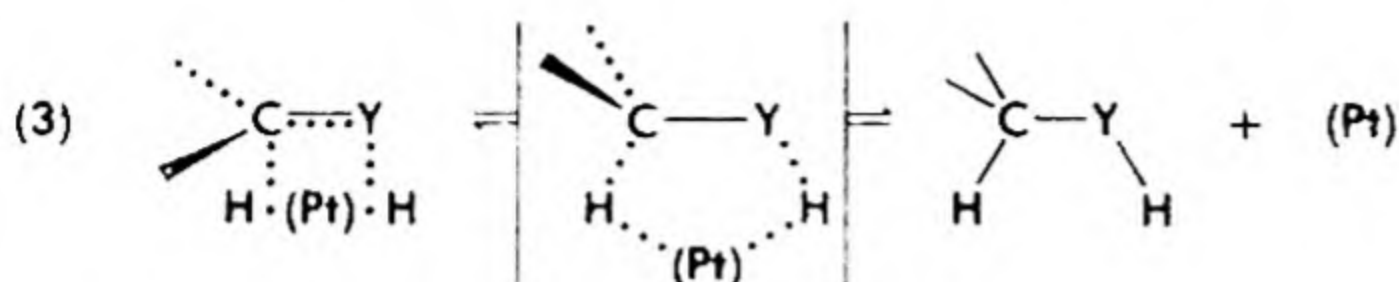
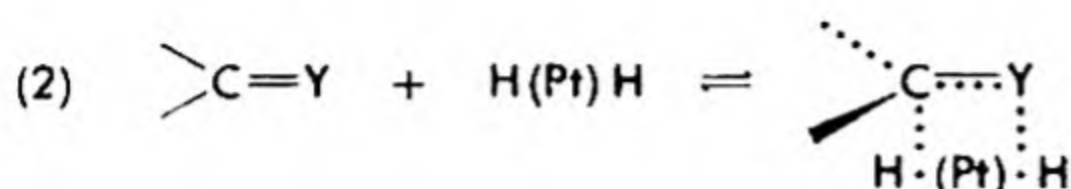


Fig. 28-1. Space Requirements for the Adsorption of a Six-Membered Carbon Ring on a Catalyst Surface.

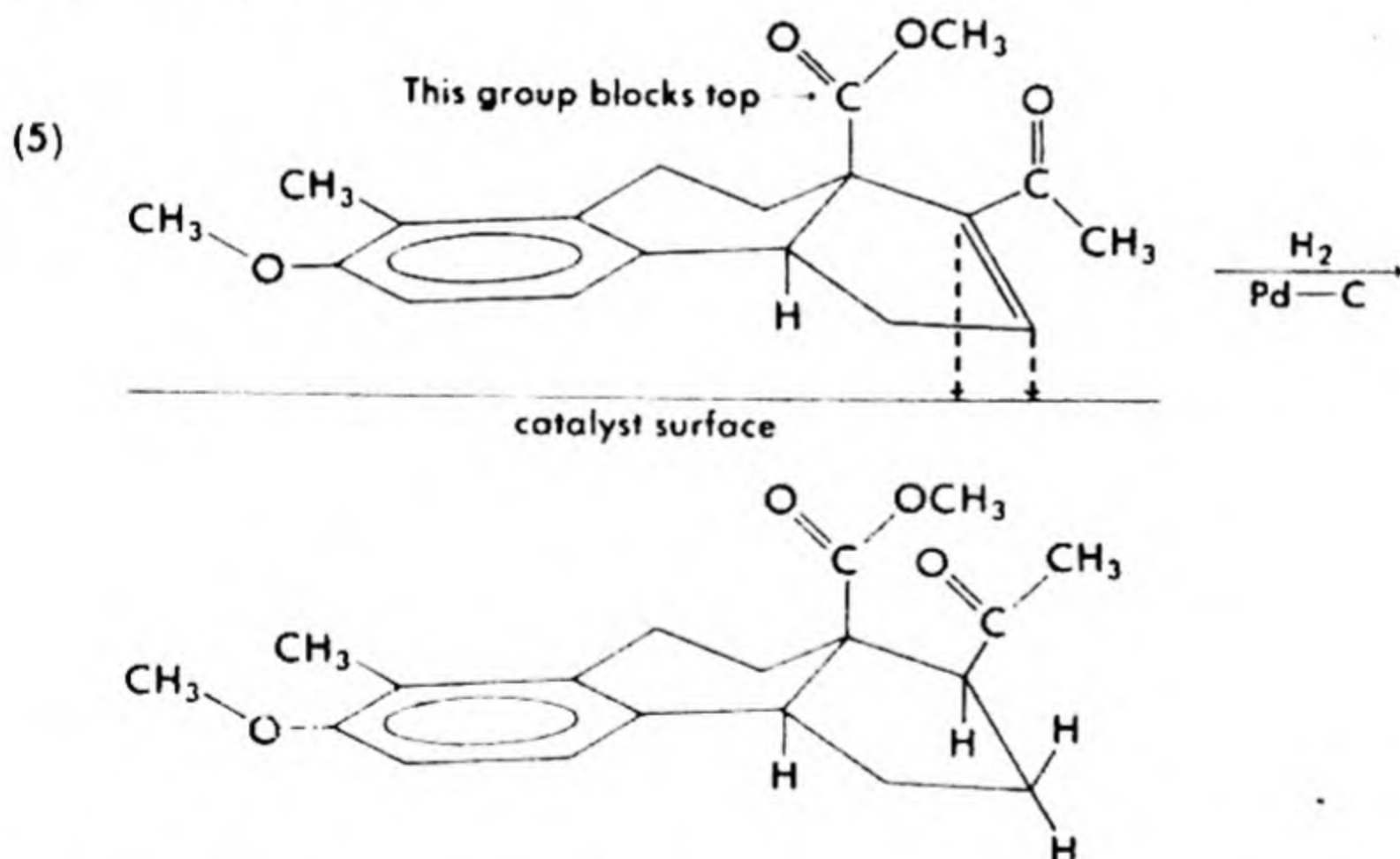
is thus adsorbed, hydrogen atoms from within the metal slide into positions where the weak π complex bonds can receive them. Both hydrogen atoms attack at essentially the same instant. In eqs. (1) through (4), (Pt) represents a surface on a platinum crystal, rather than an atom of platinum.





Only when hydrogen pressure is very low or hydrogen dissociates with difficulty on the metal (e.g., Cu), do hydrogen atoms add singly; under such circumstances, mixed configurations and polymeric products may be obtained.

An example of a stereospecific synthesis involving a hydrogenation step is outline (5).



This is one of several such stereospecific hydrogenation steps used by G. Stork and his co-workers in their synthesis of conessine, an alkaloid.

C. Hydrogenation of Unsaturated Hydrocarbons

Most olefinic double bonds can be saturated at temperatures below 200° (often at room temperature) and pressures below 100 atm. of hydrogen on Raney nickel catalyst. This is a catalyst prepared by dissolving the aluminum out of a 50-50 alloy of nickel and aluminum with sodium hydroxide. Raney nickel is very finely divided, contains dissolved hydro-

gen, and is so active that it burns vigorously if allowed to dry in air. At moderate temperatures, hydrogen does not readily attack carbonyl groups over nickel. Thus, it is possible to saturate olefinic linkages in esters, aldehydes, and ketones without destroying the carbonyl functions.

By proper choice of conditions it is possible to add a single mole of hydrogen to an acetylenic triple bond. Most alkynes add hydrogen smoothly at room temperatures and low pressures over platinum catalysts to give *cis* olefins. The requirement for stopping the reaction at the olefin stage is careful control of the amount of hydrogen used.

Aromatic rings are a different matter. Although such rings differ greatly in reactivity to hydrogenation, just as they do to other reactions, aromatic rings in general are more difficult to hydrogenate than alkenes and alkynes. Benzene must be hydrogenated in a high pressure autoclave (Fig. 28-2). Paul Sabatier, discoverer of the activity of nickel as a hydrogenation catalyst, and J. B. Senderens first hydrogenated benzene about 1900.

Hydrogenation of simple alkenes and alkynes is seldom commercially attractive, since the related alkanes are so much more readily available from petroleum or other sources. Hydrogenation of unsaturated vegetable oils produces more popular solid "shortening" (§40-1B(2)).

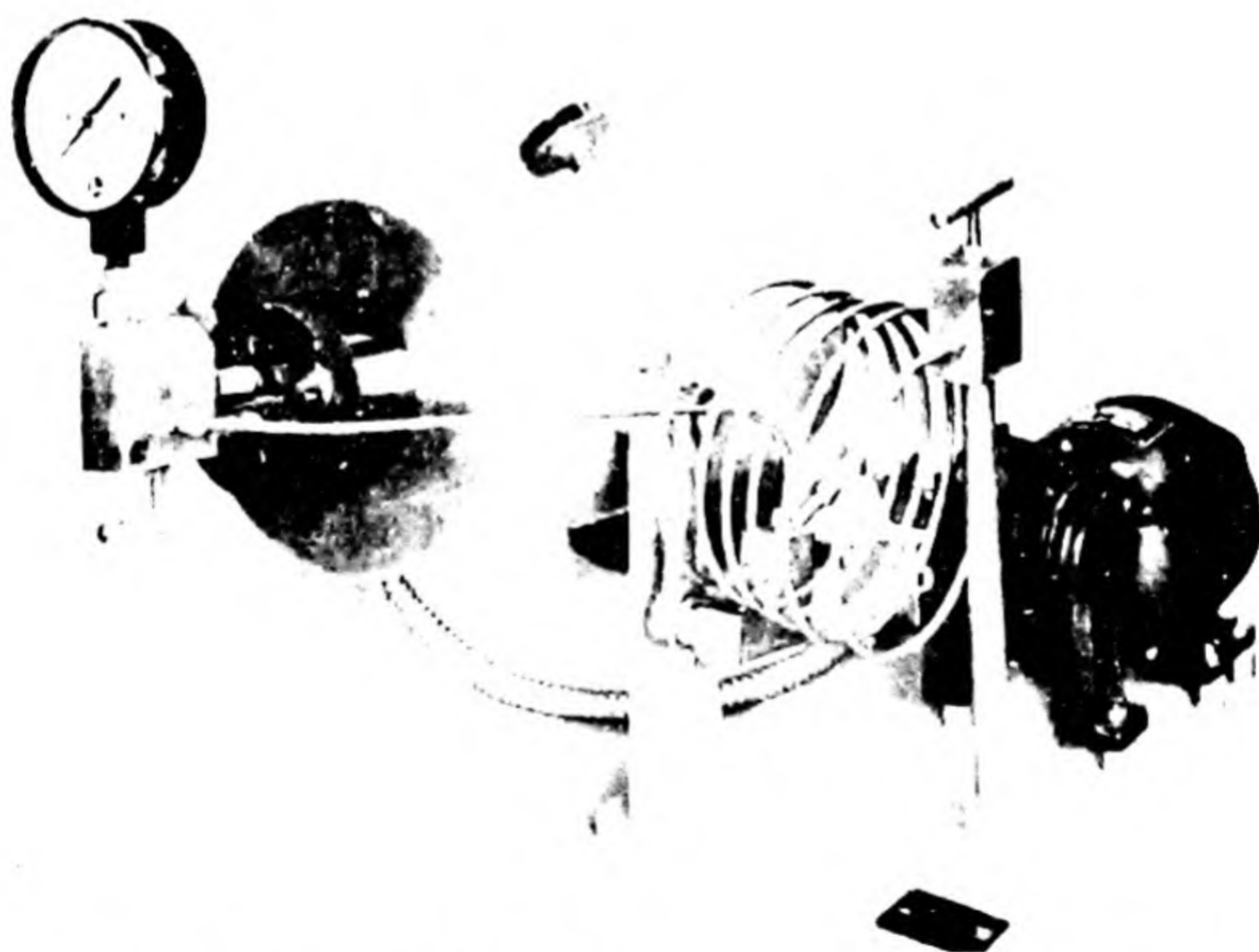
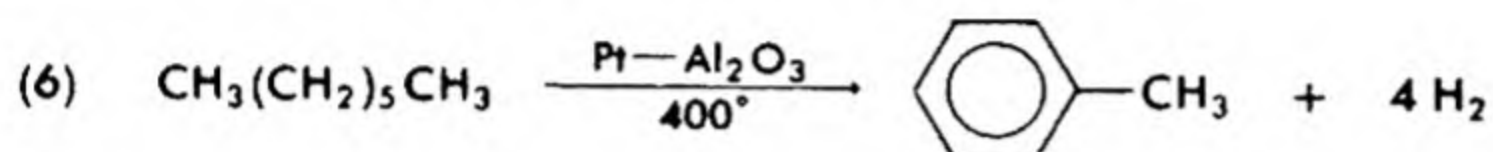


Fig. 28-2. Apparatus for High Pressure Catalytic Hydrogenation. (Courtesy of Parr Instrument Company, Moline, Ill.)

The situation with aromatic hydrocarbons is much more complex. Benzene and its homologs are in such high demand that they are prepared from cycloparaffins and alkanes by dehydrogenation. Hexanes and heptanes when heated strongly over platinum on alumina cyclodehydrogenate to benzene and toluene, respectively.

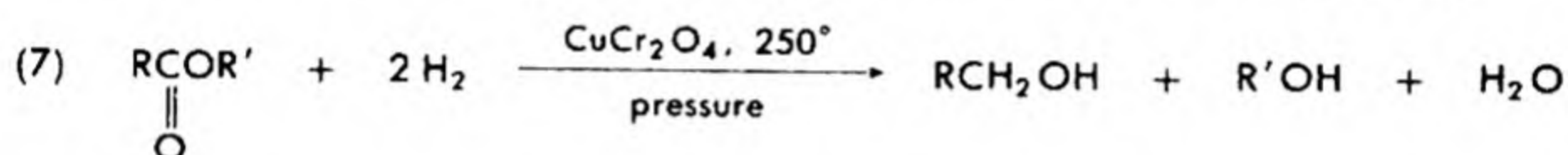


Phenol can be hydrogenated to prepare cyclohexanol, which is an intermediate in the preparation of various nylons (see §46-5B).

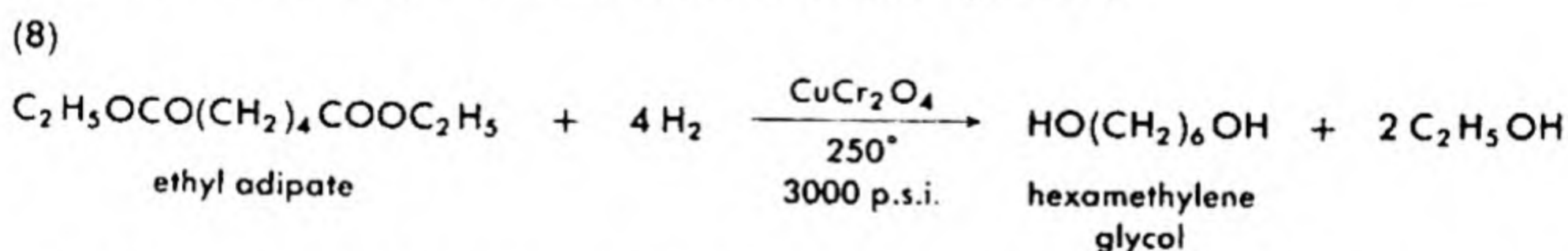
D. Hydrogenation of Polar Unsaturated Compounds

Aldehydes and ketones can be hydrogenated to alcohols, or hydrogenolyzed to hydrocarbons, depending on the conditions. Since alcohols are not readily cleaved by hydrogen unless hydrogen atoms are present on the carbon atom adjacent to the carbinol group, dehydration to an olefin is probably involved in hydrocarbon formation. Benzyl alcohols are exceptions, as benzyl-X bonds are readily hydrogenolyzed.

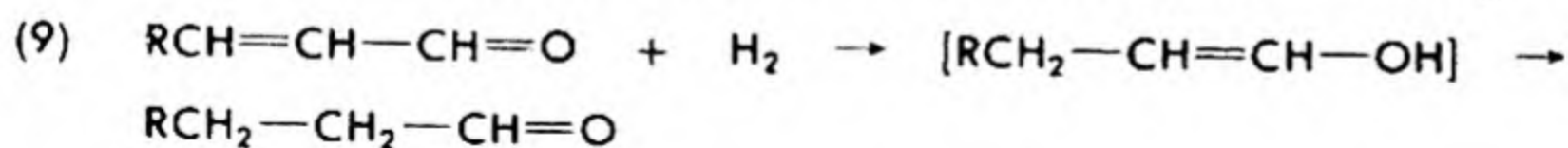
Esters also are readily hydrogenolyzed to alcohols catalytically.



This has been used both as a laboratory procedure and industrially for the preparation of diols from esters of dicarboxylic acids and for the preparation of long chain alcohols from fats (§40-3B).

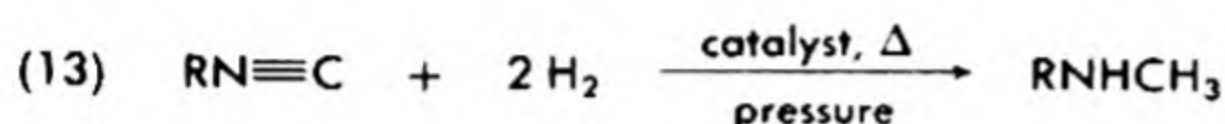
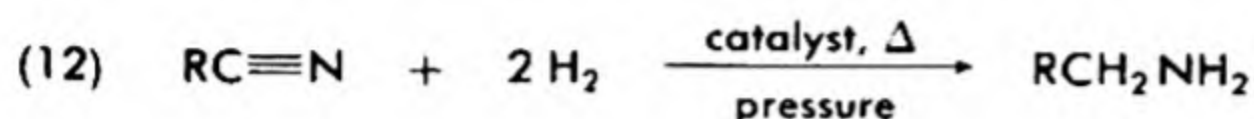
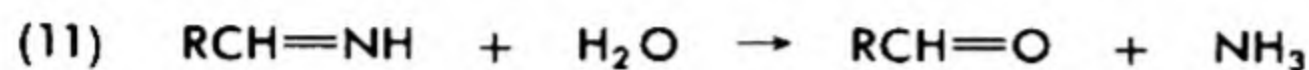
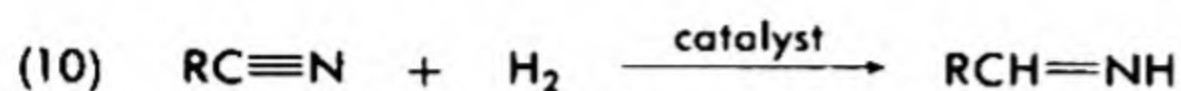


Under mild conditions, using zinc chromite catalyst, carbonyl groups and ester groups can be hydrogenated without attack upon multiple bonds in the hydrocarbon groups, unless the olefinic bonds are conjugated with the carbonyl function. In this case, 1,4-addition of hydrogen results in saturation of the olefinic unsaturation, but not the carbonyl unsaturation.

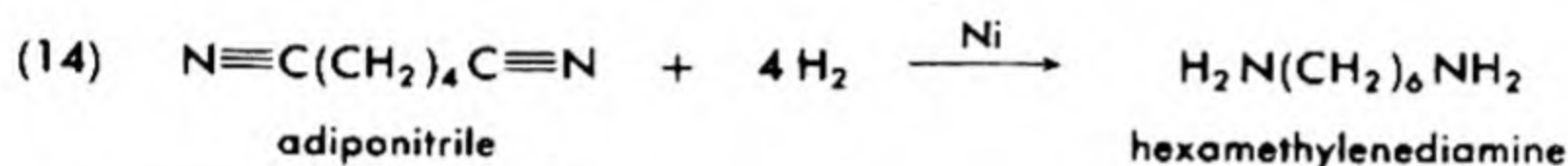


For laboratory syntheses, however, lithium aluminum hydride is more satisfactory than catalytic hydrogenation for reducing carbonyl functions in the presence of olefinic unsaturation (§20-2A).

Nitriles can be hydrogenated to aldehydes (in aqueous solution) or to primary amines. Isonitriles give methylalkylamines.

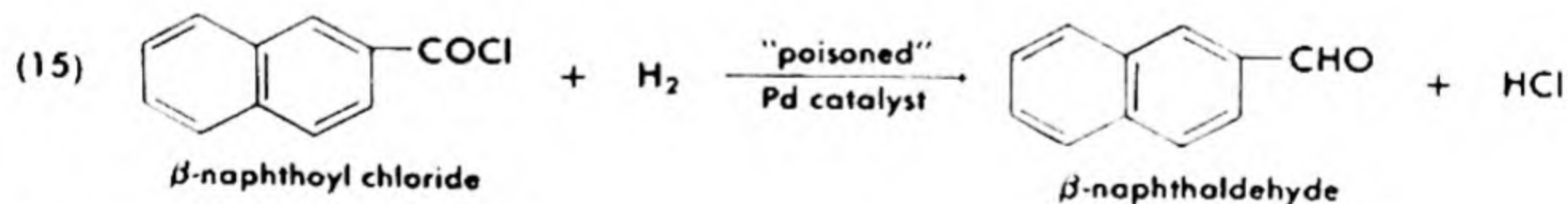


This reduction of nitriles finds much industrial application; an example is given in the preparation of hexamethylenediamine for the production of nylon 66 (§46-5B).



E. Rosenmund Reduction

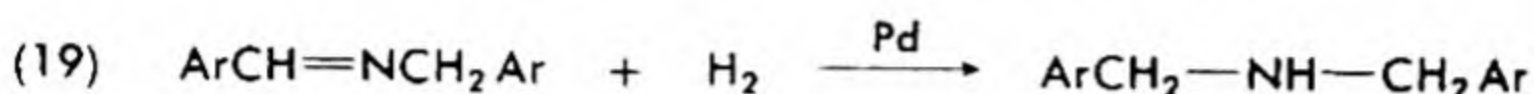
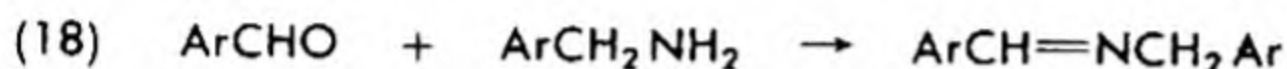
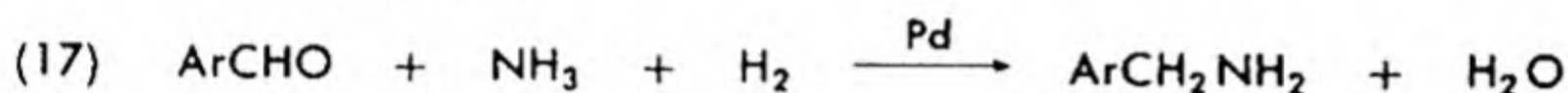
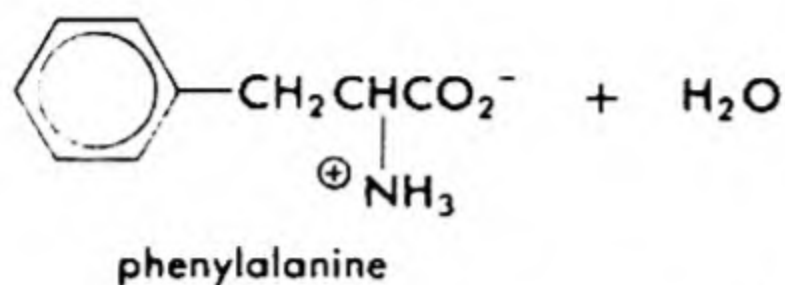
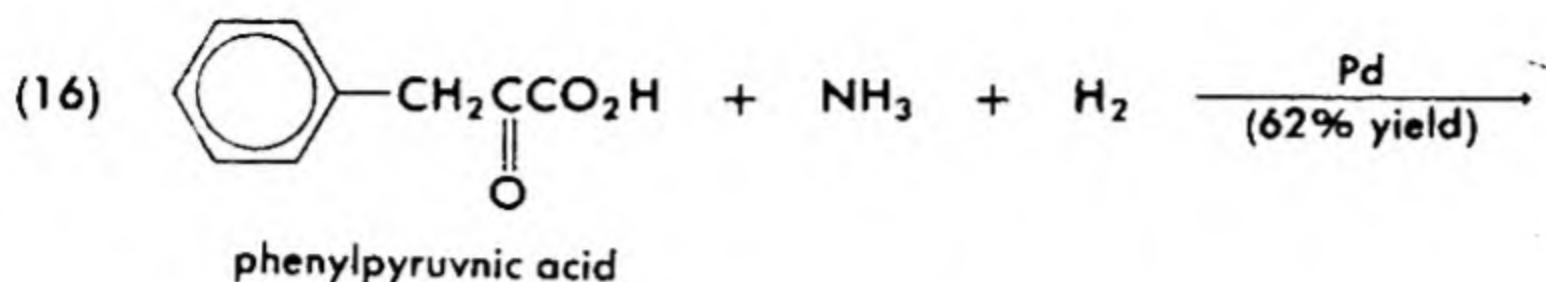
Acyl halides are more reactive toward hydrogen than aldehydes. This difference is the basis of a method of preparing aldehydes from acyl chlorides. Catalysts used for hydrogenation are very sensitive to the presence of certain materials which destroy the activity of their surfaces. For example, palladium catalyst is "poisoned" by traces of sulfur compounds and quinoline. Such a poisoned palladium catalyst is inactive in the reduction of an aldehyde, but works quite well for the hydrogenolysis of an acyl chloride. The Rosenmund method utilizes this fact to prepare aldehydes in good yield from acyl chlorides. For example, β -naphthaldehyde is prepared from the chloride in 80% yield.



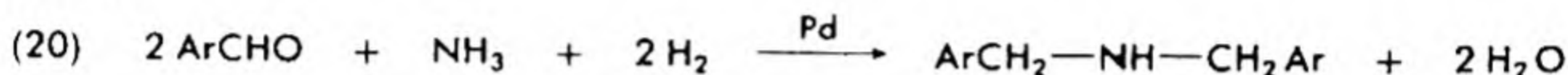
F. Reductive Alkylation

Hydrogenation of an aldehyde or ketone in the presence of ammonia or an amine can be used to prepare amines. This is one of the most satisfactory methods for preparing primary amines, and, under suitable circumstances, works very well for secondary amines.

Good yields of primary amines are favored by a large excess of ammonia. Excess of the carbonyl compound leads to tertiary amines. Secondary amines are produced in best yields when the carbonyl compound readily gives Schiff bases (imines).



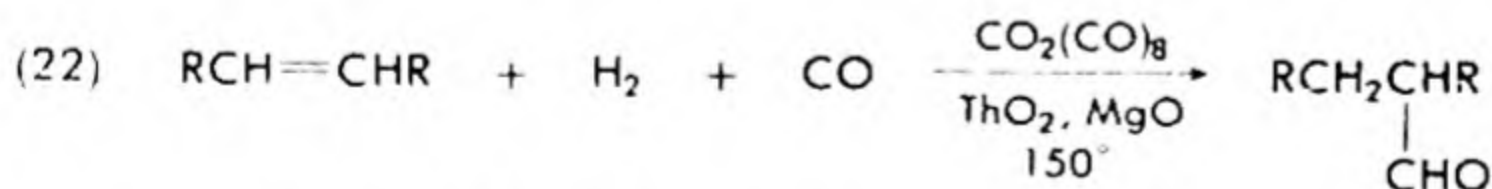
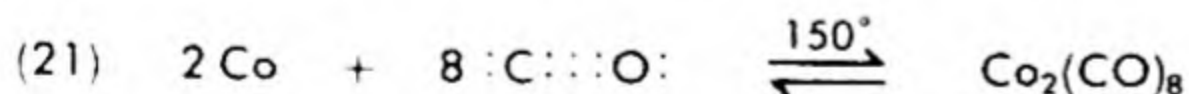
Overall:



G. The Oxo Process

Ammonia is not the only compound that can be incorporated into an unsaturated compound during hydrogenation. Olefins treated with a mixture of hydrogen and carbon monoxide in the presence of a suitable catalyst add 1 mole of each to form aldehydes. The catalyst contains (among other things) cobalt, which participates in a dual role as hydrogenation catalyst and carbonylation catalyst.

As a hydrogenation catalyst, cobalt is inferior to nickel. However, it has one advantage in this reaction, and that is its ability to form several moderately stable carbonyls. Carbonyls are coordination compounds of transition metals in which the unshared electrons on the carbon atoms of the carbon monoxide molecules coordinate with neutral metal atoms.



Aldehydes produced by the *oxo* reaction are usually hydrogenated further to alcohols in the presence of the same catalyst, but in the absence of carbon monoxide. Since carbon monoxide poisons the catalyst for hydrogenation of aldehydes, two separate steps are necessary.

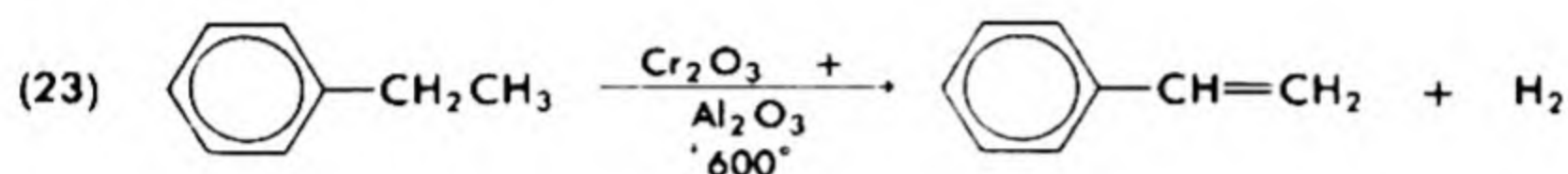
H. Reduction of Fatty Acids

The carboxyl group is very difficult to hydrogenate. All other unsaturated linkages, including aromatic rings, are reduced before the carboxyl

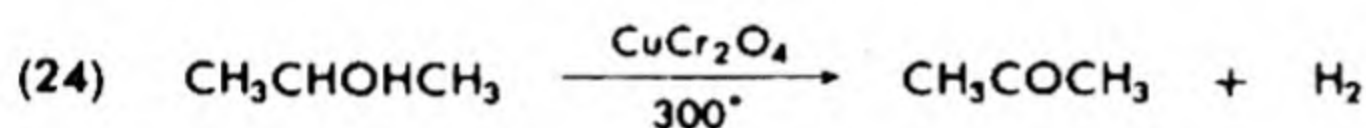
group. Hence reduction of the esters (§28-1D) is carried out industrially in the preparation of alcohols from fats.

1. Dehydrogenation

As was stated above (§28-1B), hydrogenation is a reversible process. At low hydrogen pressure, it is possible to eliminate hydrogen from saturated molecules to form unsaturated or aromatic ones. Two such processes that are commercially important are Platforming, a type of petroleum reforming (§44-1C(2)) which converts paraffins and cycloparaffins to aromatic hydrocarbons, and the dehydrogenation of ethylbenzene to styrene (eq. 23).



Dehydrogenation of an alcohol is illustrated by one industrial method of preparation of acetone (eq. 24).



SUPPLEMENTARY READINGS

- Adkins, H., and R. L. Shriner, "Catalytic Hydrogenation and Hydrogenolysis," in H. Gilman, *Organic Chemistry, An Advanced Treatise*, Vol. I, 2nd Ed., Wiley, New York, 1943, pp. 779-834.
- Emerson, W. S., "The Preparation of Amines by Reductive Alkylation," *Org. Reactions* 4, 174-255 (1948).
- House, H. L., *Modern Synthetic Reactions*, Benjamin, New York, 1965, pp. 1-22.
- Komaresky, V. I., C. H. Riesz, and F. L. Morritz, "Catalytic Reactions," in A. Weissberger, *Technique of Organic Chemistry*, Vol. 2, 2nd Ed., Wiley, New York, 1956, pp. 94-164.
- Mosettig, E., and R. Mozingo, "The Rosenmund Reduction of Acid Chlorides to Aldehydes," *Org. Reactions*, 4, 362-377 (1948).

QUESTIONS AND PROBLEMS

1. Define the following terms:

- | | |
|-------------------|-------------------------|
| a. reduction | d. catalyst poison |
| b. hydrogenation | e. reductive alkylation |
| c. hydrogenolysis | f. hydroformylation |

2. Write equations for reactions that occur under the specified conditions with the reagents listed. Use structural formulas for organic compounds.

- | | |
|--|---|
| a. 3-butenal, 1 mole of hydrogen, nickel | b. 3-butenal, 1 mole of hydrogen, zinc chromite |
|--|---|

- | | |
|--|---|
| c. crotonaldehyde, 1 mole of hydrogen, zinc chromite | g. methyl <i>n</i> -caproate, hydrogen, cupric chromite at 200° |
| d. isovaleroyl chloride, excess hydrogen, palladium | h. benzophenone, hydrogen, ammonia, palladium |
| e. cyclohexanecarbonyl chloride, hydrogen, poisoned palladium catalyst | i. benzophenone, excess hydrogen, nickel at 200°, 200 atm. |
| f. methyl <i>n</i> -caproate, hydrogen, cupric chromite at 150° | j. stilbene, hydrogen, carbon monoxide, cobalt catalyst |

3. Show how the following compounds can be prepared in good yield from the suggested starting materials. Use structural formulas for organic compounds. Indicate essential reagents and conditions.

- 2-ethylpentyl 2,4-dichlorophenoxyethanoate from 3-hexene, phenol, and acetic acid
- phenylglycine (2-amino-2-phenylethanoic acid) from benzoic acid
- 4-¹⁴C-butanoic acid from ¹⁴C-sodium carbonate and appropriate organic compounds
- 3,4-dideuteriopentanal from butadiene
- adipic acid from hexane via benzene

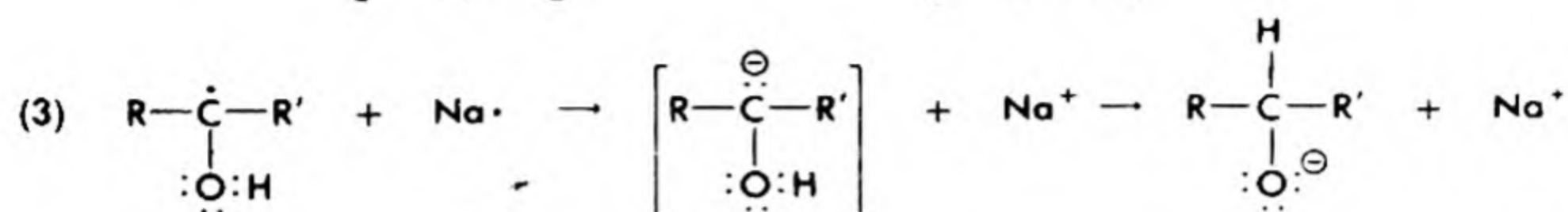
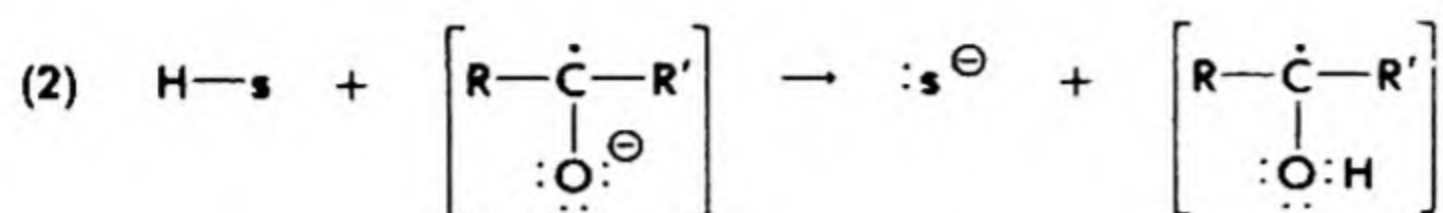
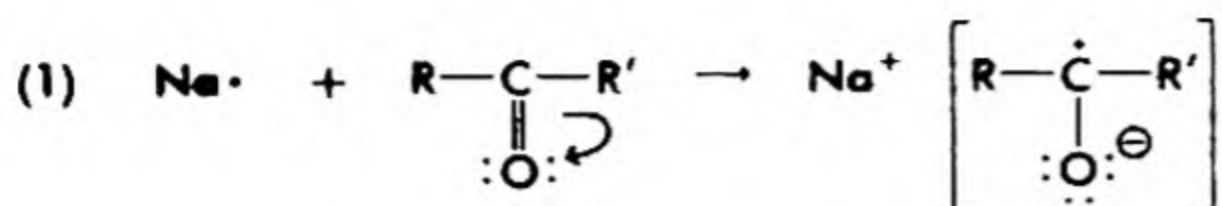
28-2 REDUCTION BY METALS

Since metals are electron donors, it may be expected that electrophilic groups, such as carbonyl, nitro, and halogen, are more susceptible to metallic reduction than nucleophilic groups, such as olefinic or acetylenic linkages.

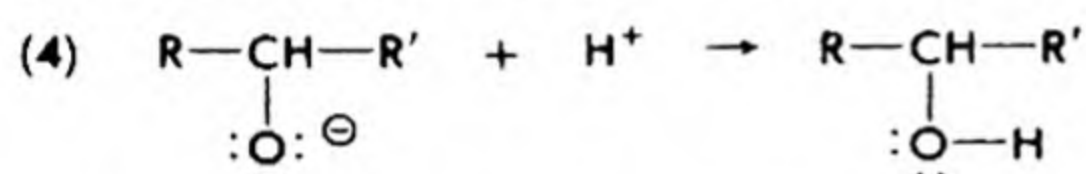
A. Mechanisms of Metallic Reductions

It is well known that metals which are good reducing agents react with water or acids to give hydrogen. However, the fact that many metallic reductions give results entirely different, both in ease of reduction and in type of product, from those of catalytic hydrogenation make it clear that the two types of processes are different. Three different mechanisms of metallic reduction are discussed below.

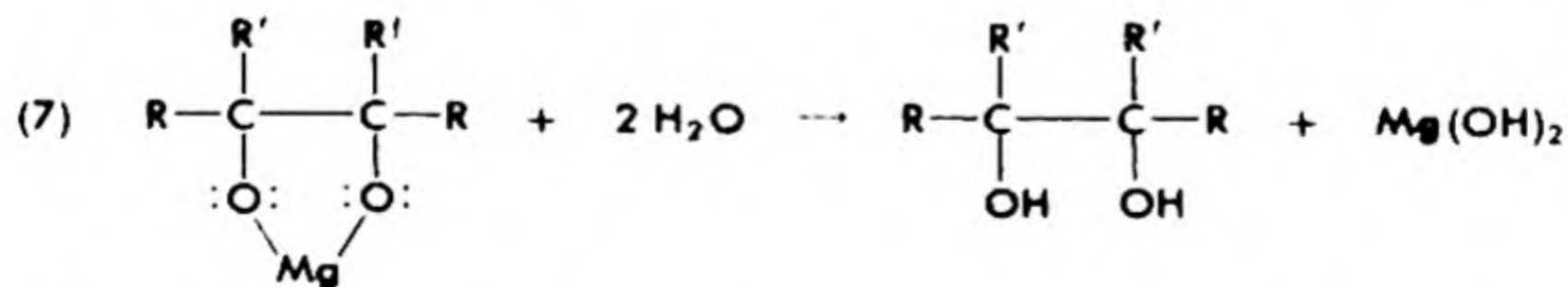
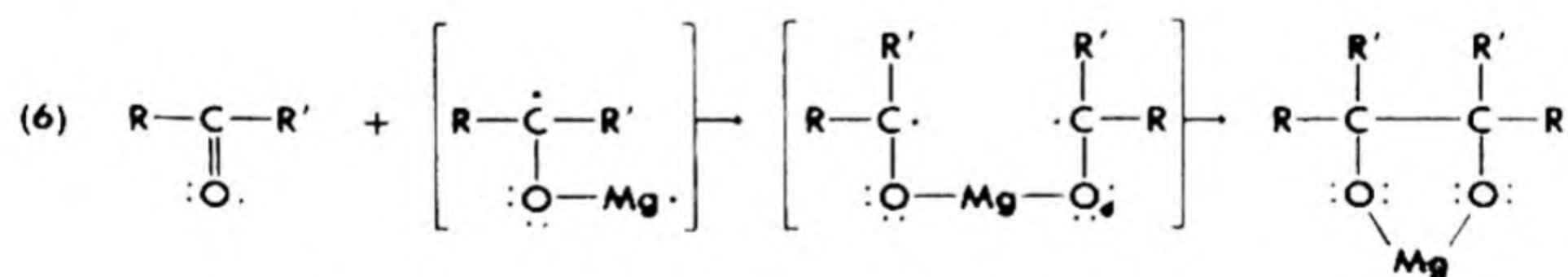
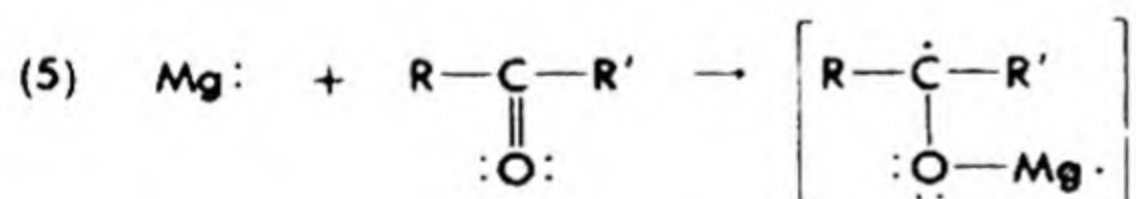
Carbonyl compounds can be reduced by either of two mechanisms. The kind of metal, the nature of the carbonyl group, and the environment influence the course of the reaction. One mechanism is unimolecular reduction to alcohols; the other, bimolecular reduction to glycols (pinacol reduction). In either case, the first step is doubtless donation of an electron from the metal to the carbon atom of the carbonyl group (eq. 1). What follows depends on how closely associated two such occurrences are and the availability of protons from the solvent. With monovalent metals, the probable independence of different occurrences of this step favors intervention by a hydrogen ion from the solvent (eq. 2) before reaction with a second metal atom (eq. 3).



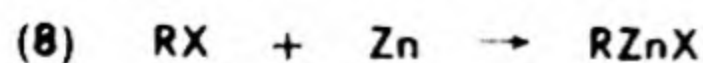
Neutralization of the mixture by an acid then gives the alcohol related to the original carbonyl compound.

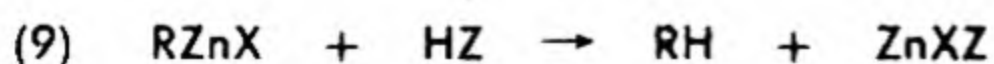


In the second mechanism, if the radical ion initially formed by the carbonyl compound is held in an inert solvent while another is formed immediately at the same location, the two radicals may be induced to join together. Such a reaction is favored by the use of a bivalent metal, such as magnesium, and a nonacid solvent, such as benzene. The magnesium is amalgamated to prevent formation of a coating on its surface.



The third mechanism is concerned with the reduction of halides to hydrocarbons. An organometallic compound may be an intermediate.

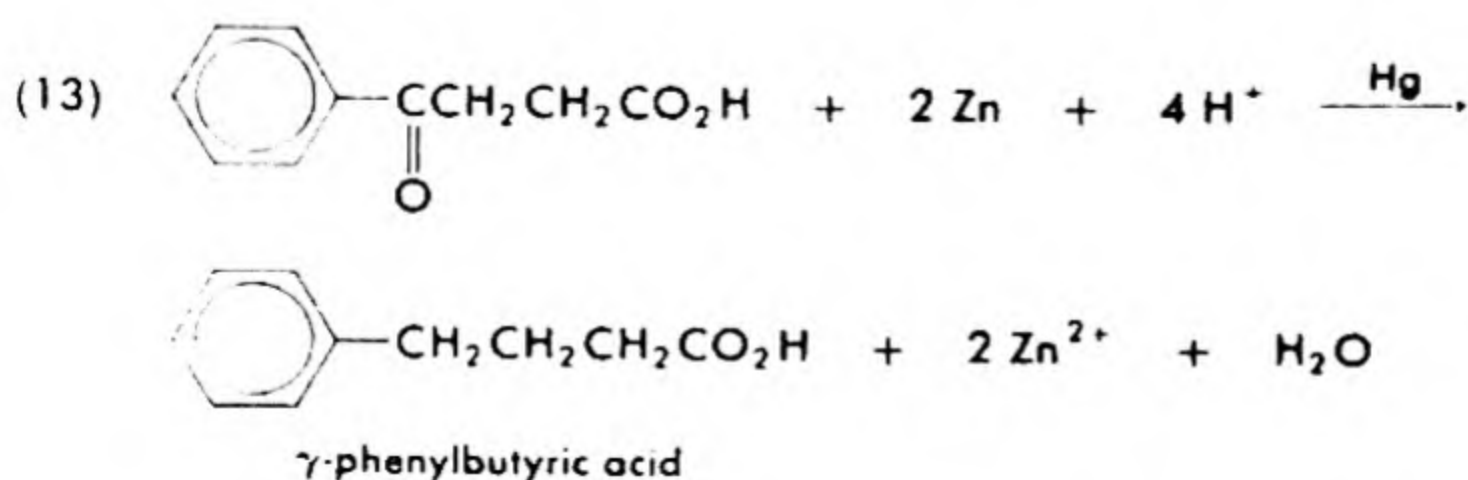
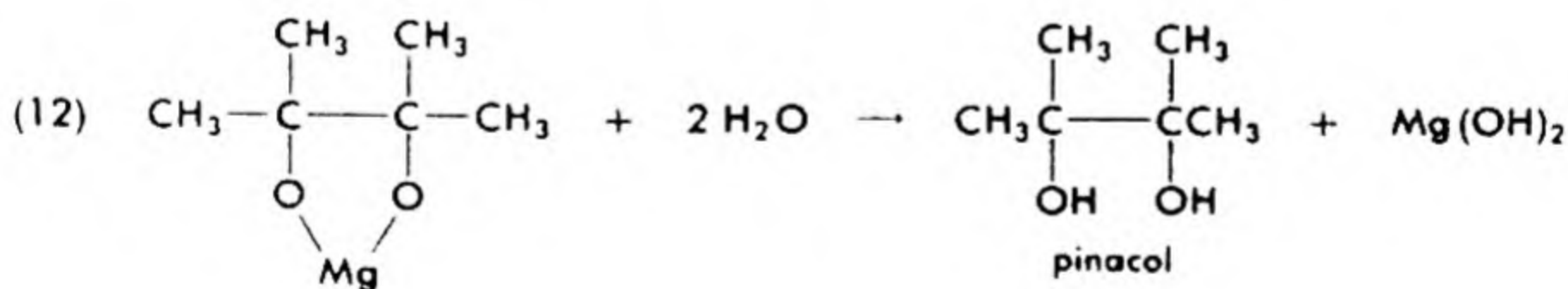
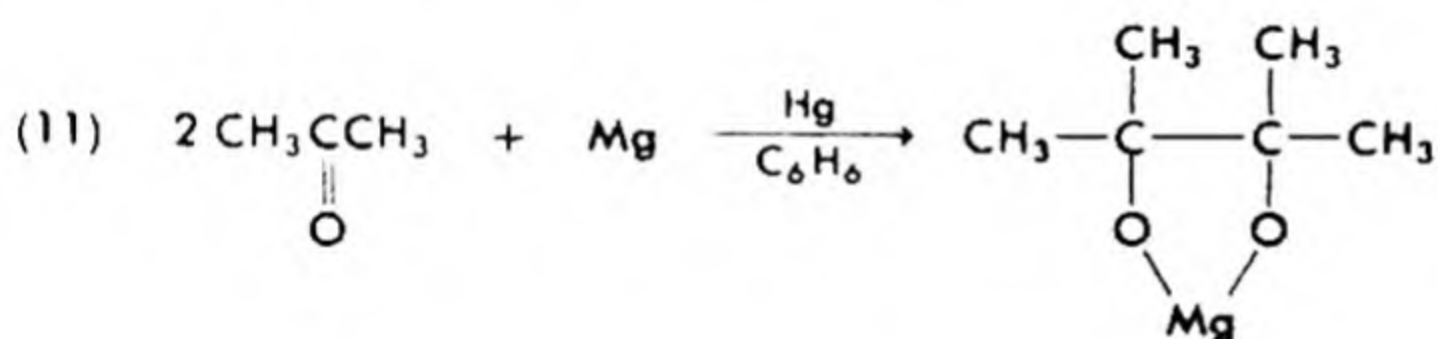
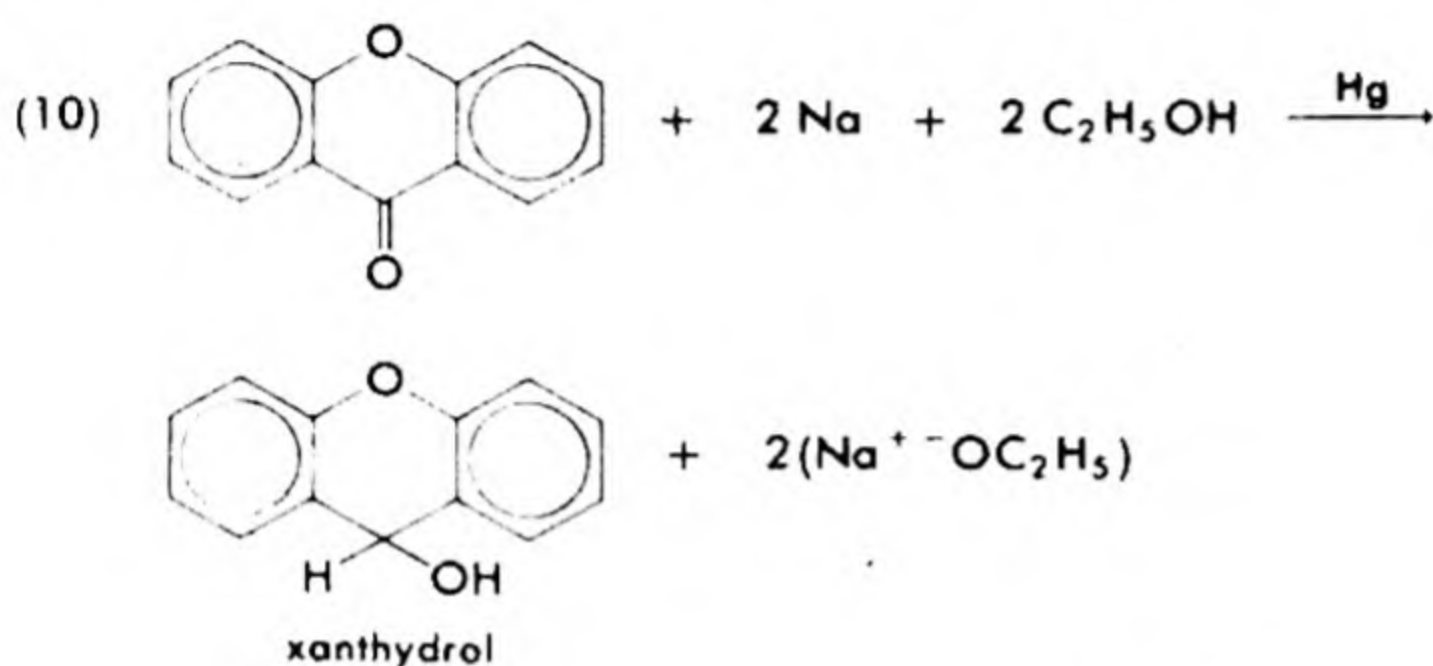


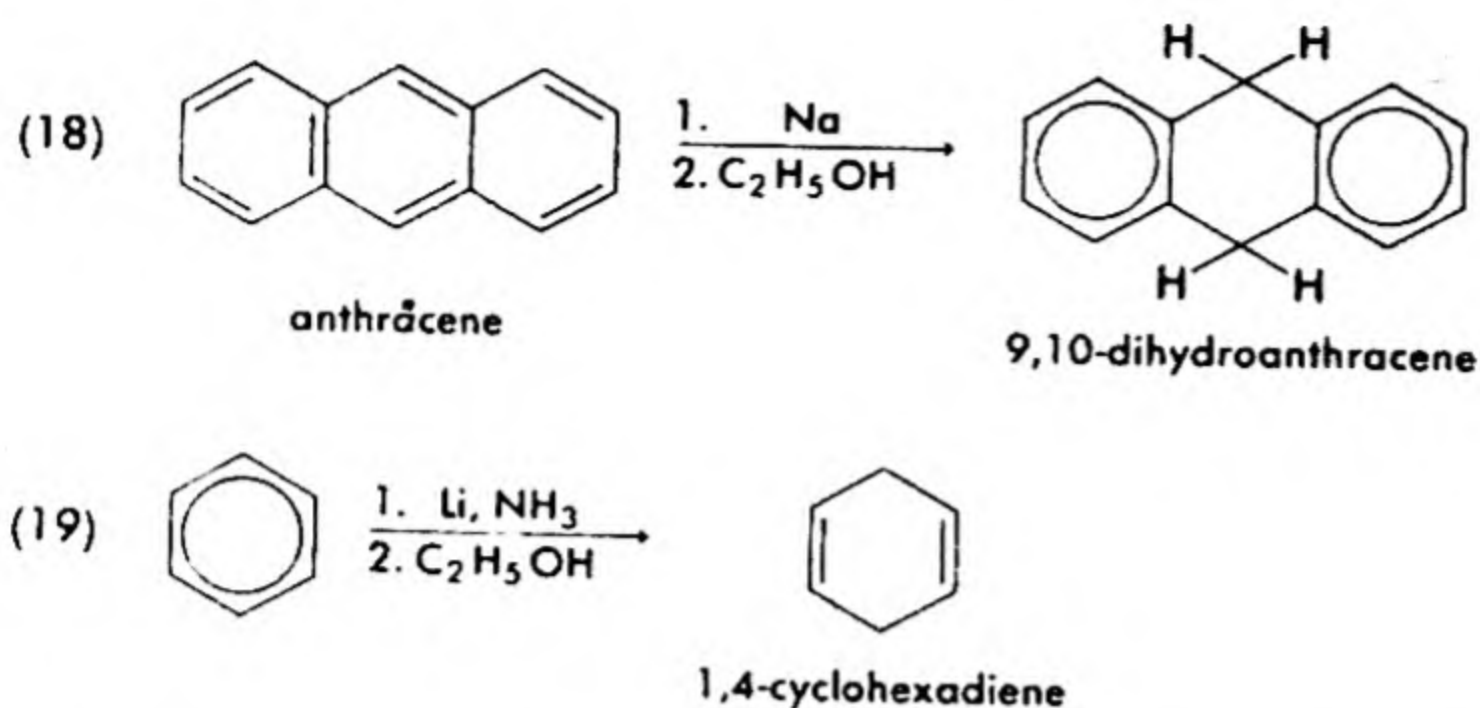


A number of important metallic reduction procedures are utilized for which the mechanism has not yet been established. The *Clemmenson reduction* of aldehydes and ketones by zinc amalgam in acid is one of these. The carbonyl group becomes a methylene group in all but a few cases, yet alcohols are not generally reduced under the same conditions, so that the carbinol is certainly not an intermediate.

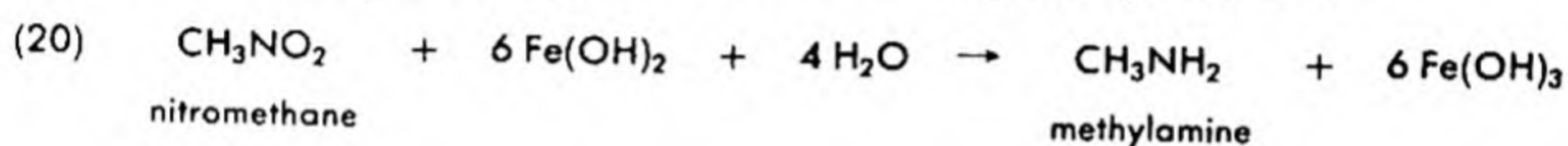
B. Representative Reductions

Reactions representative of the reduction of carbonyl compounds are the preparation of xanthydrol in 91–95% yield, pinacol in 43–50% yield (based on magnesium), and γ -phenylbutyric acid in 90% yield.





The strength of nitro compounds as oxidizing agents is one of their more notable properties. A simple test for such an oxidizing group in the molecule is to shake it with freshly prepared ferrous hydroxide in a test tube in which air has been displaced by a nonoxidizing gas, such as illuminating gas. Oxidation of iron(II) to iron(III) is observed in the conversion of blue ferrous hydroxide to brown ferric hydroxide.



SUPPLEMENTARY READINGS

- Birch, A. J., "The Reduction of Organic Compounds by Metal-Ammonia Solutions," *Quart. Rev.*, **4**, 69-93 (1950).
 Birch, A. J., and H. Smith, "Reduction by Metal-Amine Solutions: Applications in Synthesis and Determination of Structure," *Quart. Rev.*, **12**, 17-33 (1958).
 House, H. O., "Modern Synthetic Reactions," Benjamin, New York (1965), pp. 50-77.
 Martin, E. L., "The Clemmenson Reduction," *Org. Reactions* **1**, 155-209 (1942).

QUESTIONS AND PROBLEMS

1. Write equations for the reactions which occur among the following reagent mixtures. Use structural formulas for organic compounds and indicate essential conditions.

- | | |
|--|---|
| a. butyraldehyde, sodium amalgam, and water | e. α -bromoacetoacetic acid, amalgamated zinc, and hydrochloric acid |
| b. acetophenone and amalgamated magnesium in anhydrous benzene | f. benzaldoxime, sodium amalgam, and water |
| c. mesityl oxide, amalgamated zinc, and hydrochloric acid | g. 2-nitro-2-propanol, iron, and hydrochloric acid |
| d. diacetone alcohol, amalgamated | |

2. Show how the following compounds can be prepared in good yield from the suggested starting materials. Use structural formulas for organic compounds. Indicate reagents and essential conditions.

- | | |
|--|---|
| a. 2-ethyl-1,3-butylenediamine
from ethanol and ethyl acetate | d. ethylcyclobutane from propylene
and ethyl acetoacetate |
| b. 1,1,2,2-tetraphenylethane-1,2-
diol from benzoic acid | e. 2-methylbenzene-1,3,5-tri-
carboxylic acid from toluene |
| c. cyclohexane from pimelic acid | |

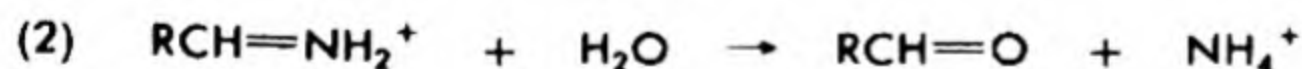
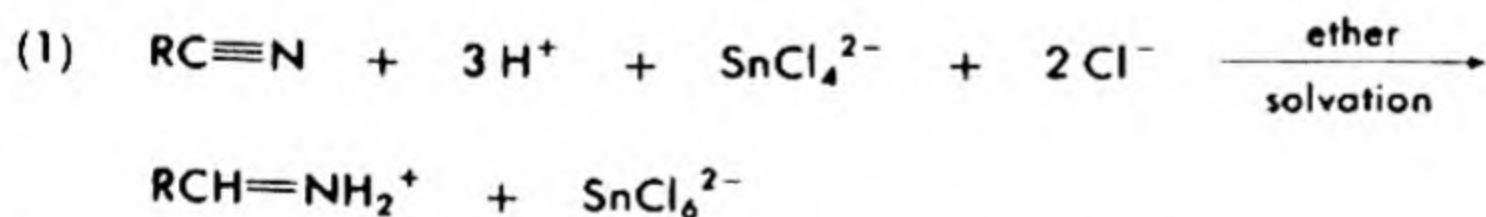
28-3 MISCELLANEOUS REDUCING AGENTS

A collection of various reducing agents with important specific applications which, however, come under none of the more general classifications remain to be considered. Mechanisms of their actions are not included since most of them have not received the attention that more general reagents have. Some methods discussed elsewhere (§20-2–§20-2B and §23-3) should be recalled.

A. Lower Valence Compounds of Metals with Several Valences

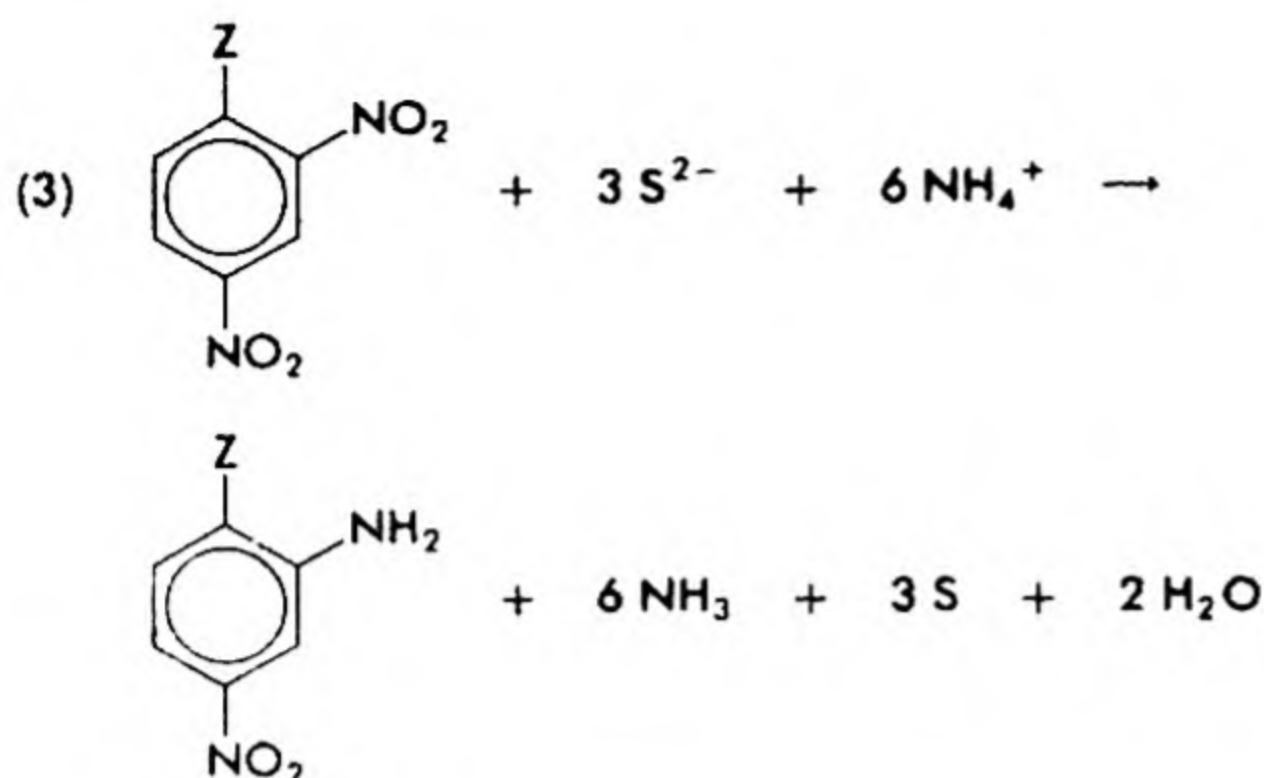
The ability of ferrous hydroxide to reduce nitro compounds, nitrates, nitroso compounds, and quinones was mentioned as a qualitative test for such strong oxidizing groups. Thus far, ferrous hydroxide has received little application in synthesis.

Stannous chloride and hydrochloric acid, combined in anhydrous ether to form chlorostannous acid, is the reagent in the *Stephen reduction* of nitriles to aldehydes. The intermediate imine hydrochlorides, probably in the form of double salts with the tin salts, are hydrolyzed by the addition of water. The aldehyde is then steam distilled from the complex of tin and ammonium chlorides remaining. Stannous chloride is also effective for the reduction of nitro compounds to amines.



B. Ammonium Sulfide Reduction of Nitro Compounds

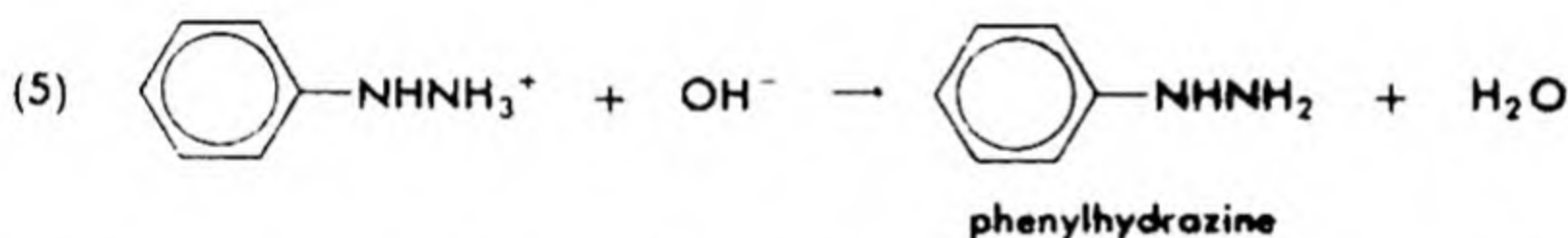
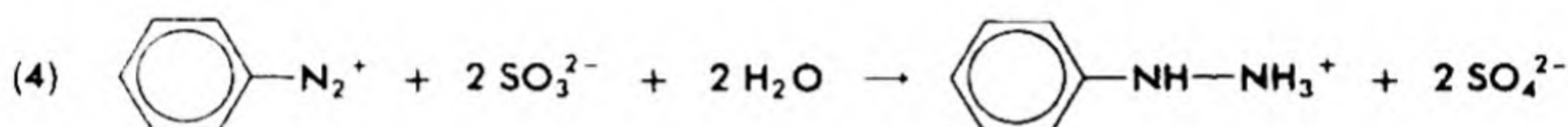
One of two nitro groups on a benzene ring can be reduced to an amino group by the use of aqueous sodium sulfide and ammonium chloride. Yields of 4-nitro-2-aminophenol and 4-nitro-1,2-phenylenediamine from the corresponding dinitro compounds are reported to be near 60%.



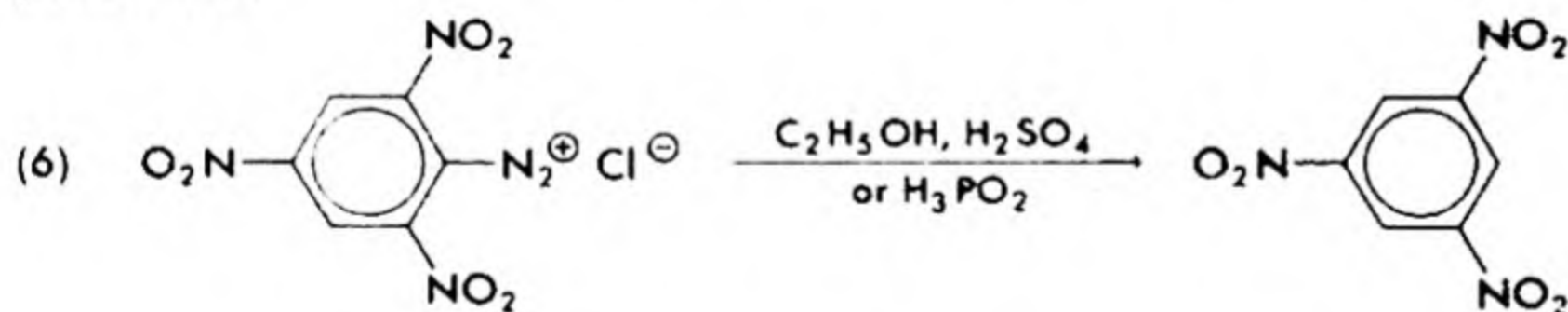
Z = OH, NH₂

C. Reduction of Diazonium Groups

The reduction of diazonium salts to hydrazines can be accomplished by the use of sodium sulfite. Phenylhydrazine is so prepared from aniline in 84% overall yield.



An acidic ethanol solution or hypophosphorous acid can be used to remove the diazonium group completely (outline 6). Both are free radical processes.



QUESTIONS AND PROBLEMS

1. Write equations for the reactions that occur in the following reagent mixtures. Use structural formulas for organic compounds. Indicate essential conditions.

- a. benzoyl cyanide, stannous chloride, and hydrogen chloride
- b. 2,4-dinitro-5-methylphenol, sodium sulfide, and ammonium

- c. *p*-ethoxyphenyldiazonium chloride and sodium sulfite

2. Show how the compounds listed below can be prepared in good yield from the suggested starting materials. Use structural formulas for organic compounds. Indicate reagents and essential conditions.

- | | |
|---|--|
| a. tridecanal from lauryl alcohol | c. 4-nitro-1,2-phenylenediamine
from benzene |
| b. cyclohexanecarbaldehyde from cyclohexane | d. 2-chloro-5-nitrophenylhydrazine
from benzene |

REVIEW PROBLEM

1. Show how the following compounds can be prepared in acceptable yield from the indicated starting materials and inorganic reagents. All organic intermediates are to be made from the designated starting materials. Use structural formulas for organic compounds. Indicate reagents and essential conditions.

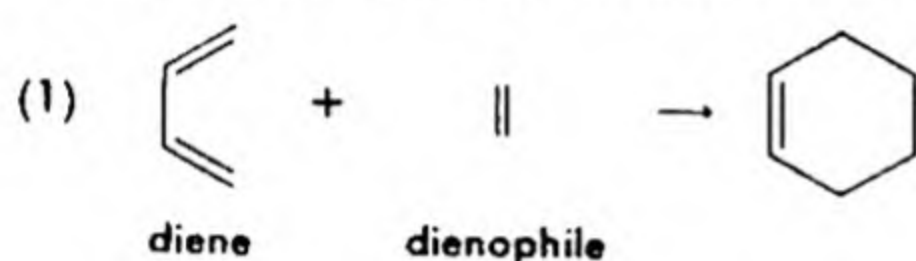
- | | |
|--|---|
| a. 1-amino-2-propanol from ethanol | f. 4-fluorophenylhydrazine from aniline |
| b. terephthalaldehyde (1,4-benzene-dicarbaldehyde) from <i>p</i> -nitroaniline | g. 1- ¹⁴ C-phenol from pentamethylene bromide and sodium ¹⁴ C-carbonate |
| c. 1,3-cyclohexanediol from <i>m</i> -dinitrobenzene | h. phenyl triphenylmethyl ketone from benzophenone |
| d. cyclopentadiene from cyclopentanone | i. trimethylacetic acid (pivalic acid) from acetone |
| e. 3,4-dimethyl-3-hexanol from 2-butene | |

29

Cycloadditions

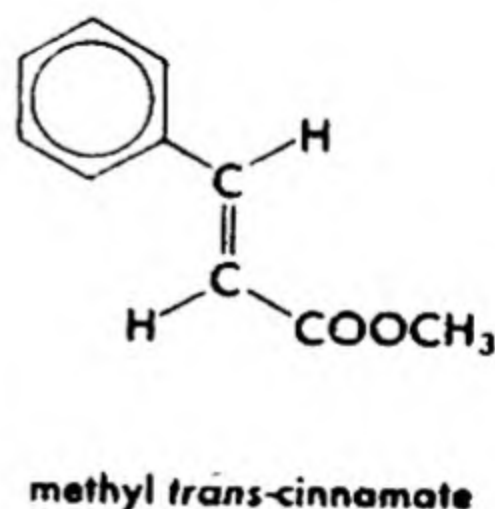
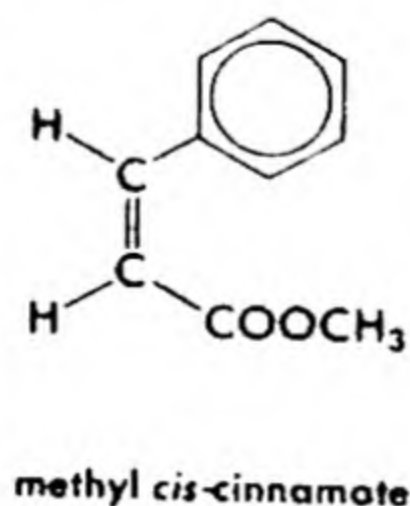
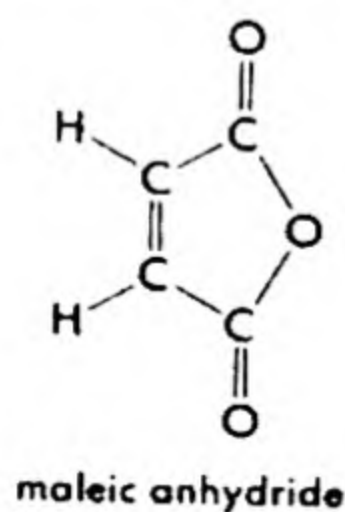
29-1 DIENE SYNTHESIS

Otto Diels and Kurt Alder (Nobel laureates, 1950) were the codevelopers of the reaction bearing their name, in which a conjugated diene adds an unsaturated compound. The reaction, generalized in eq. (1), is an important example of 1,4-addition. It represents a very useful procedure for the synthesis of a six-membered ring.



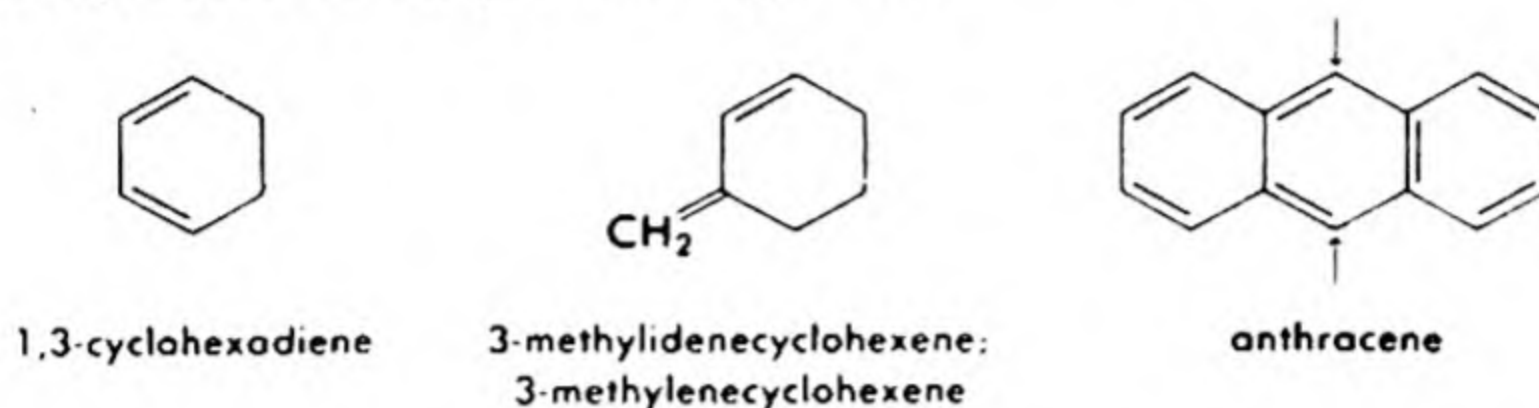
A. Dienophiles

The compounds which add to dienes are called dienophiles. These include principally compounds containing carbon-carbon double bonds or carbon-carbon triple bonds, although some other multiple bond systems are reactive. Ethylene and acetylene themselves are reactive with some dienes; multiple bonds conjugated with activating groups (e.g., carbonyl, cyano, aryl, nitro) are more reactive. The reaction suffers from steric strains; hence trisubstituted olefins are difficultly reactive and tetrasubstituted ones are usually unreactive. *cis*-Disubstituted olefins are more reactive than *trans* for similar reasons. Thus, maleic anhydride is a very reactive dienophile and methyl *cis*-cinnamate is considerably more reactive than methyl *trans*-cinnamate.



B. Dienes

Acyclic conjugated dienes and cyclic conjugated dienes in which the double bonds lie on the same side of the single bond (such as cyclohexadiene) that separates them may react with dienophiles. When the double bonds are held in the *transoid* position (e.g., 3-methylidenecyclohexene), reaction is proscribed on geometric grounds.



Double bonds that are parts of benzene rings do not ordinarily react. Thus benzene and styrene are inert as dienes. However, fused benzene ring compounds are reactive, albeit under severe conditions. Thus, anthracene reacts at the 9,10 positions as shown, as the loss in resonance energy is minimized compared with reaction at other positions.

C. Conditions of Reaction

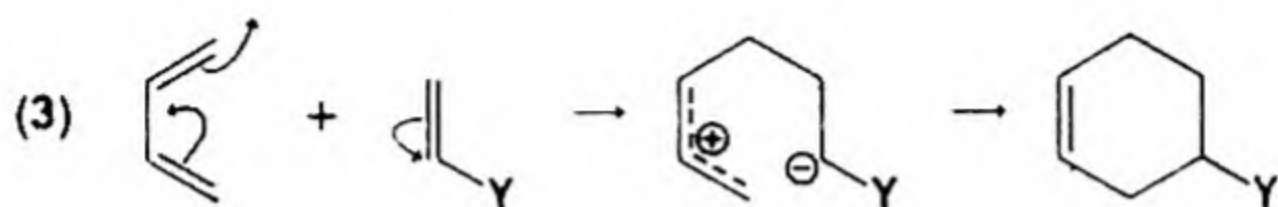
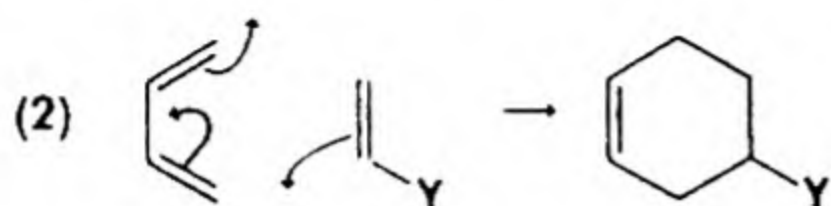
The Diels-Alder reaction occurs with or without a solvent and can occur in the vapor phase.

Temperatures of reaction vary considerably. Temperatures from -10° to 300° have been used. Maleic anhydride often adds quite vigorously even at low temperatures. Quinones react best in the range from 90° to 110° . Temperatures higher than this are necessary with unactivated olefins and usually with sluggish dienes such as anthracene. Many of the additions are reversible and proceed in the reverse direction at higher temperatures.

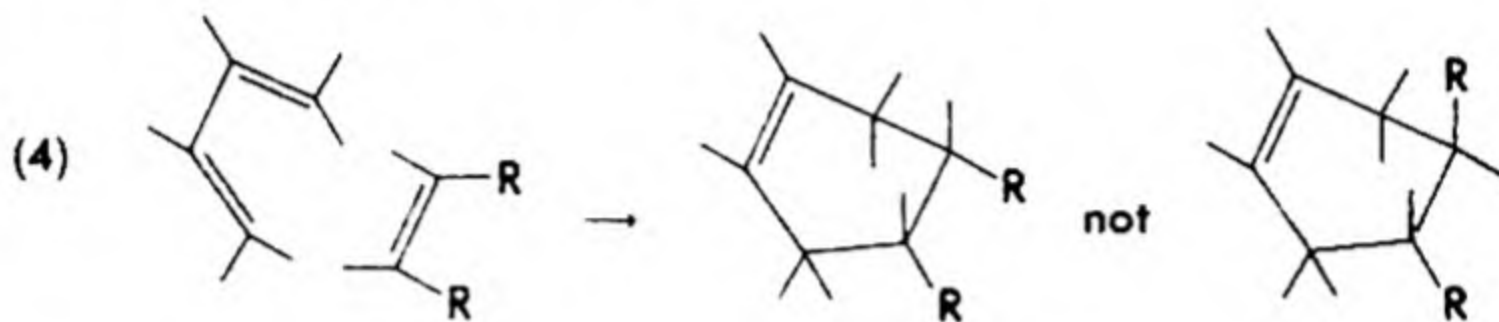
Some diene syntheses are subject to catalysis, but this is not general. One of the characteristics of the reaction is that a catalyst is unnecessary. Indeed, the avoidance of certain types of impurities, or their inhibition, is essential to prevent polymerization as a side reaction. Often it is advantageous to include some hydroquinone or other free radical trap in the reaction mixture to inhibit the polymerization of the olefin or diene.

D. Mechanism and Rules of Isomer Formation

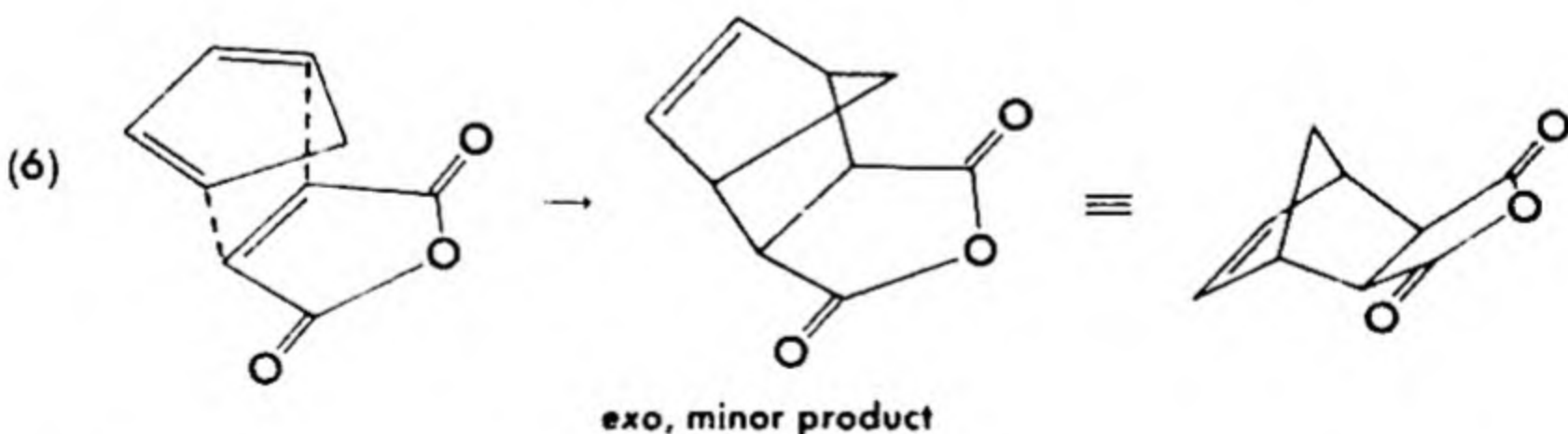
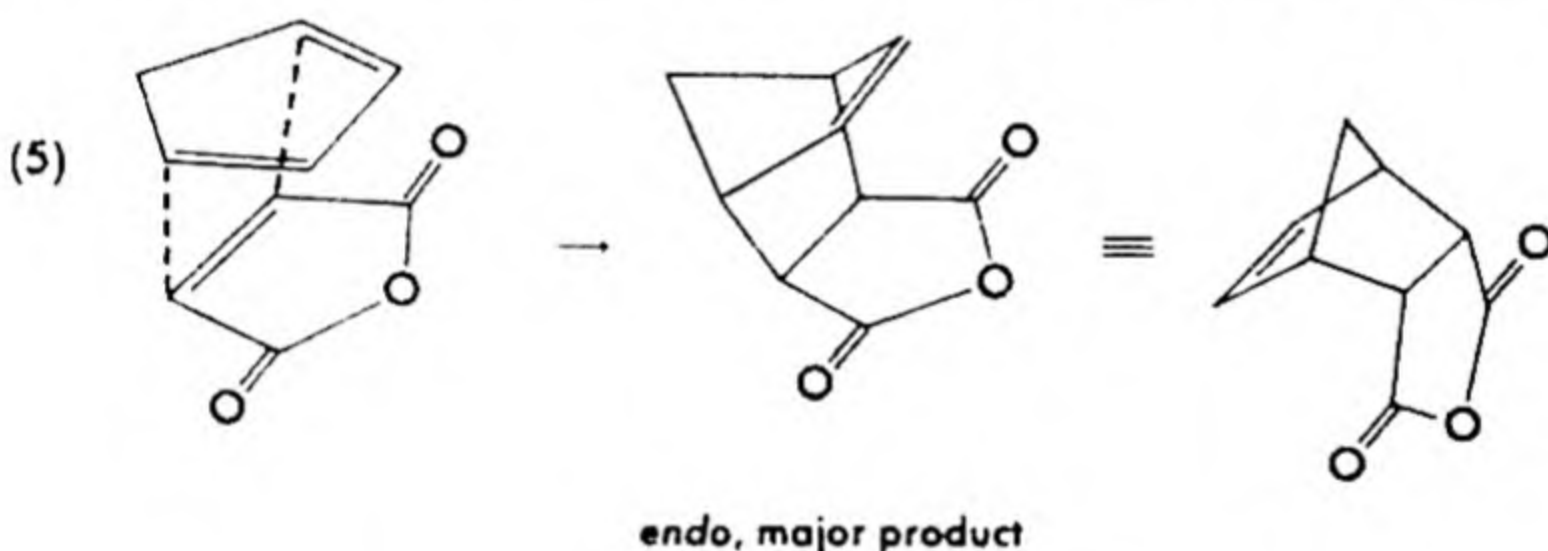
The diene synthesis is an example of the ease of formation of six-membered rings. It is not clear whether all the bonds are made and broken at one time (eq. 2), whether reaction occurs first at one end and then at the other (eq. 3), or whether there are examples of both types. It would appear that electron pair shifts are involved, at least in those cases where acid catalysis is observed.



Certain orientation rules apply to the synthesis. Addition always occurs *cis* to the dienophile (eq. 4).

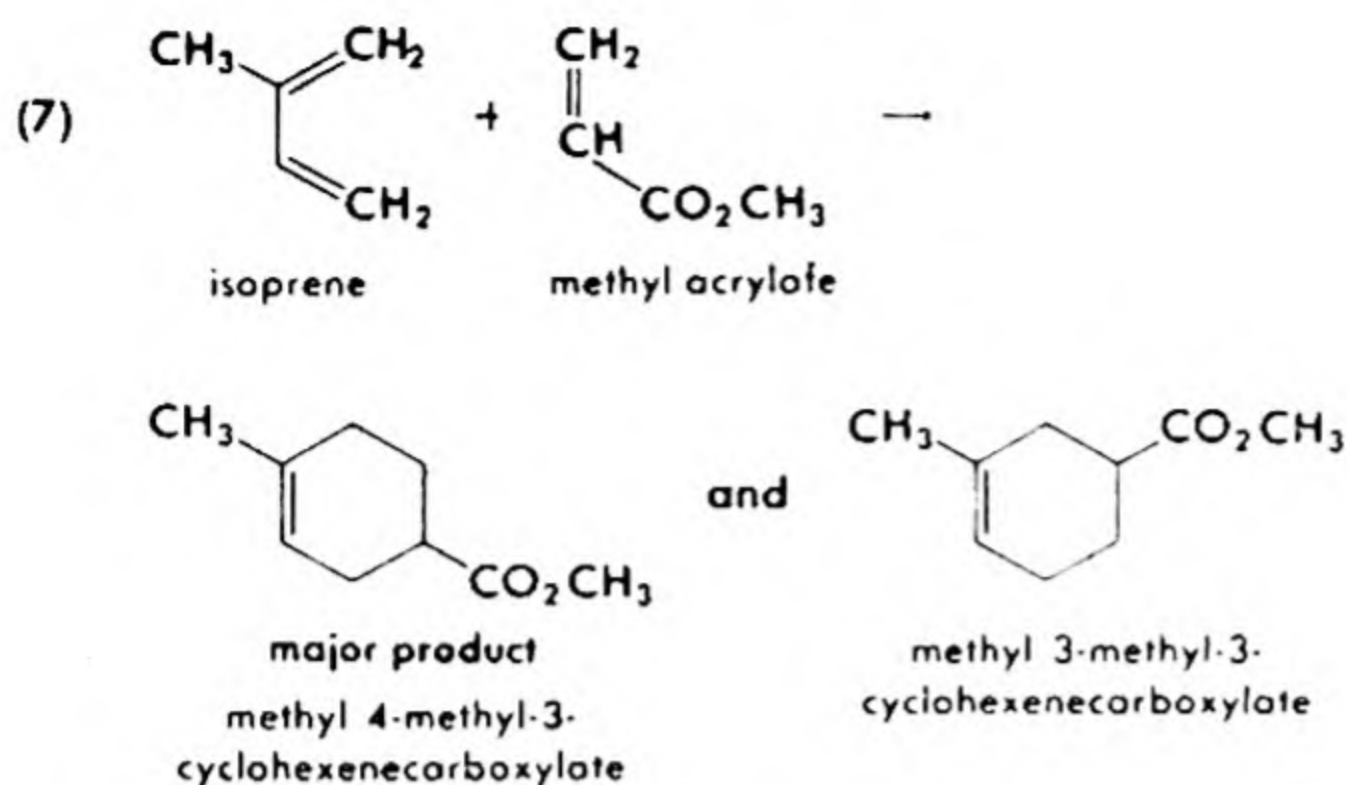


Addition of cyclopentadiene to a dienophile occurs to give predominantly *endo* addition, involving positions of the interacting molecules which give maximum interactions of π orbitals in the unsaturated systems.

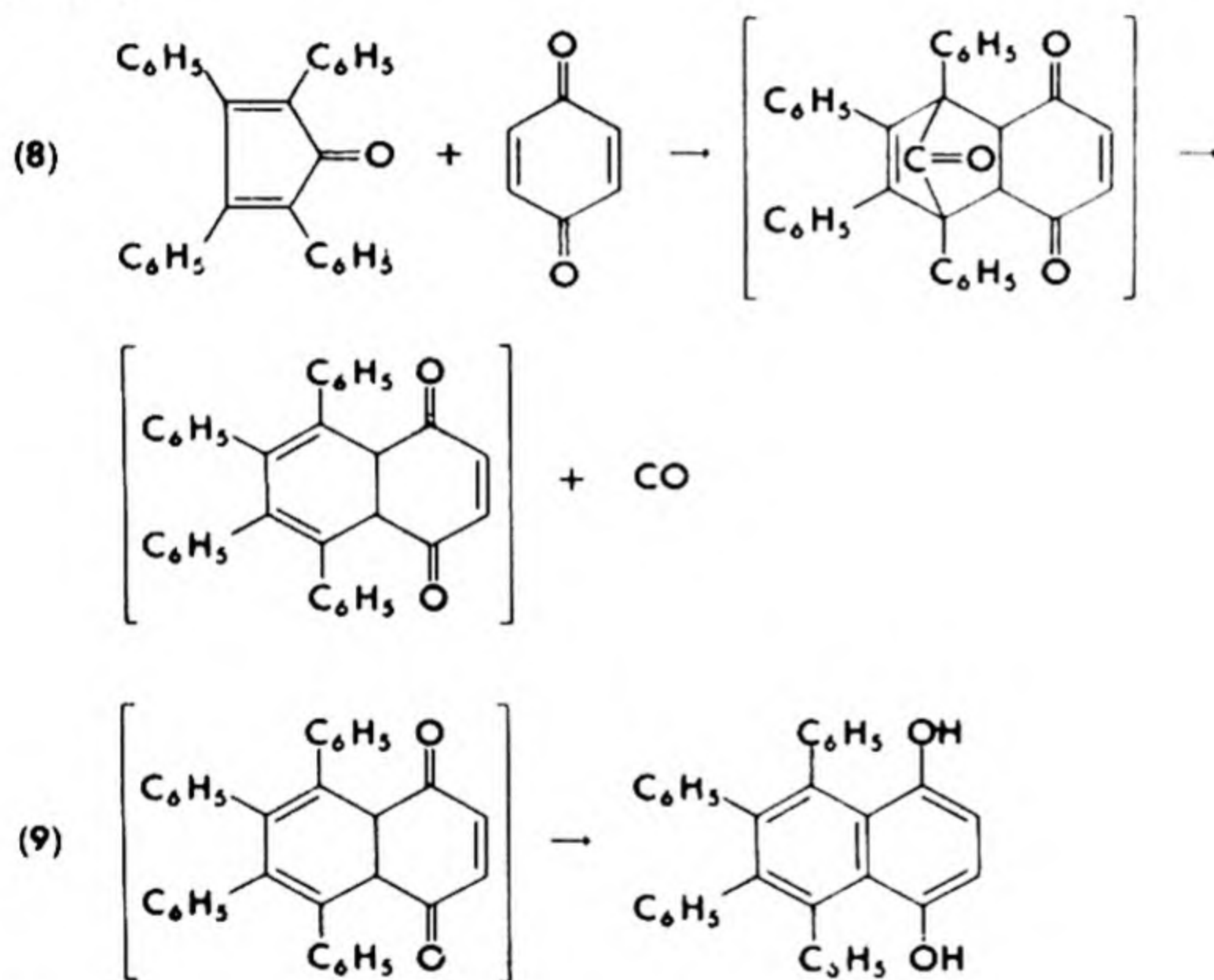


In cases where isomers may be formed, it is generally true that both result. Thus isoprene and methyl acrylate give a mixture (outline 7).

The reversibility of the Diels-Alder reaction should be emphasized. The stability of the products depends on the nature of the groups. Nevertheless, at some sufficiently high temperature, decomposition to the starting materials may occur, provided other decomposition does not occur first.



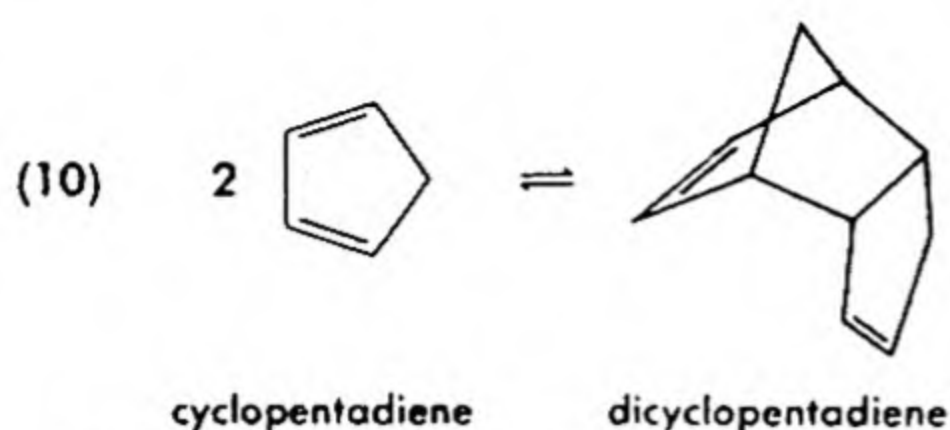
Certain decompositions other than reversal of the diene synthesis are exceptionally easy, such as elimination of a bridging carbonyl group (eq. 8).



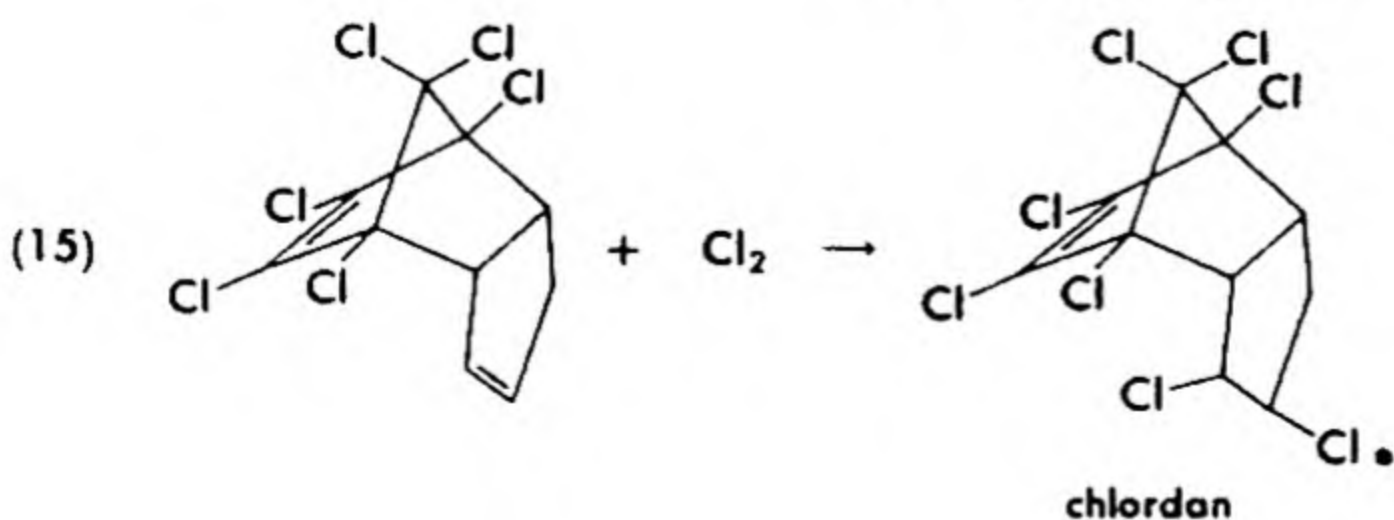
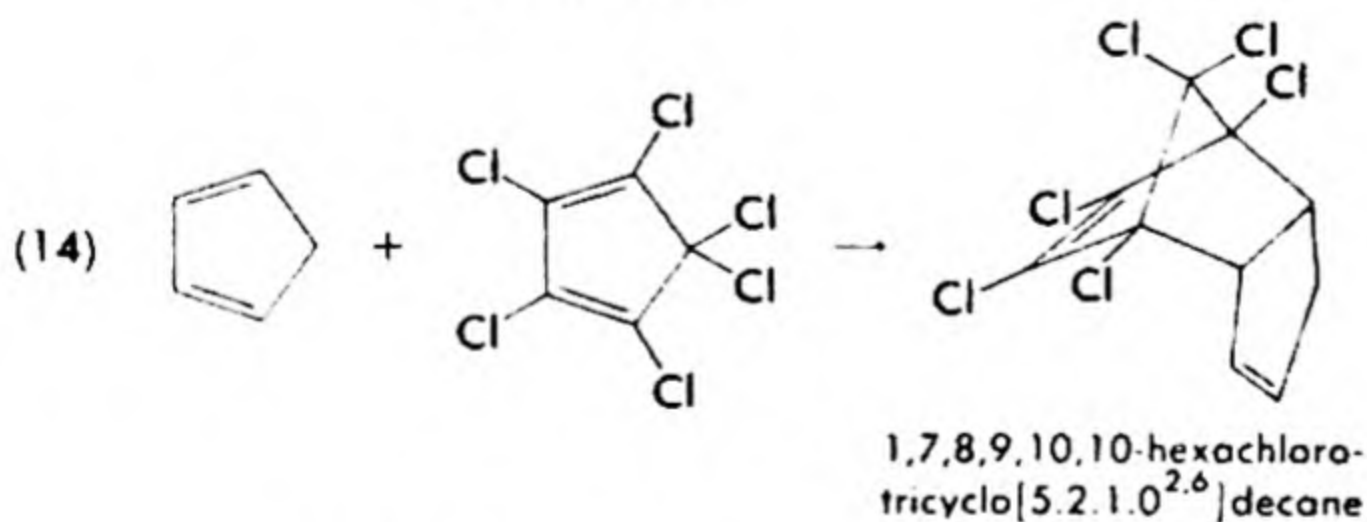
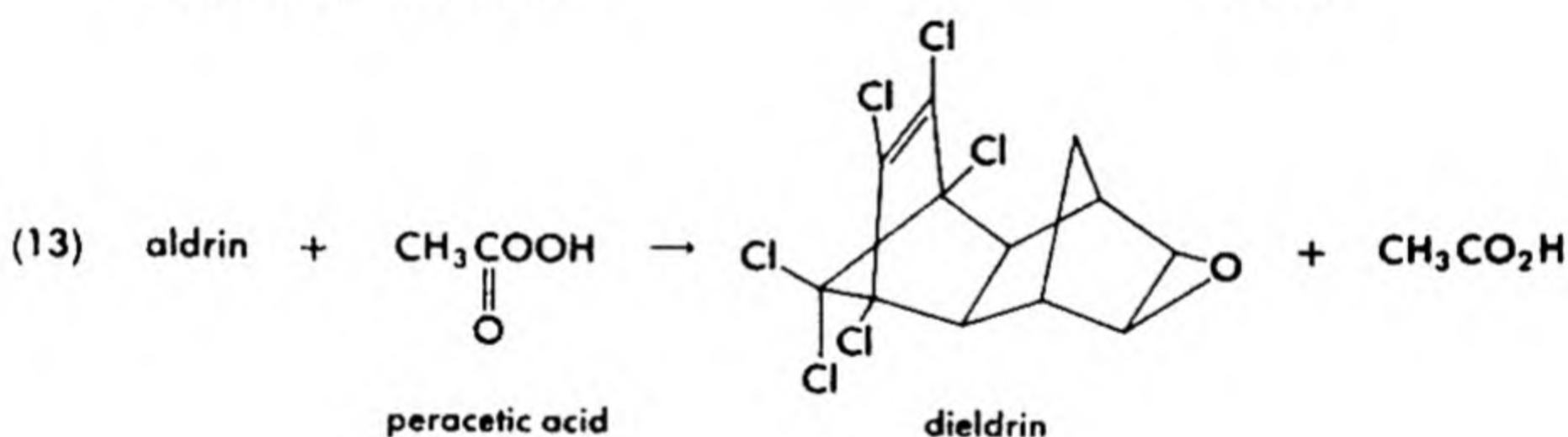
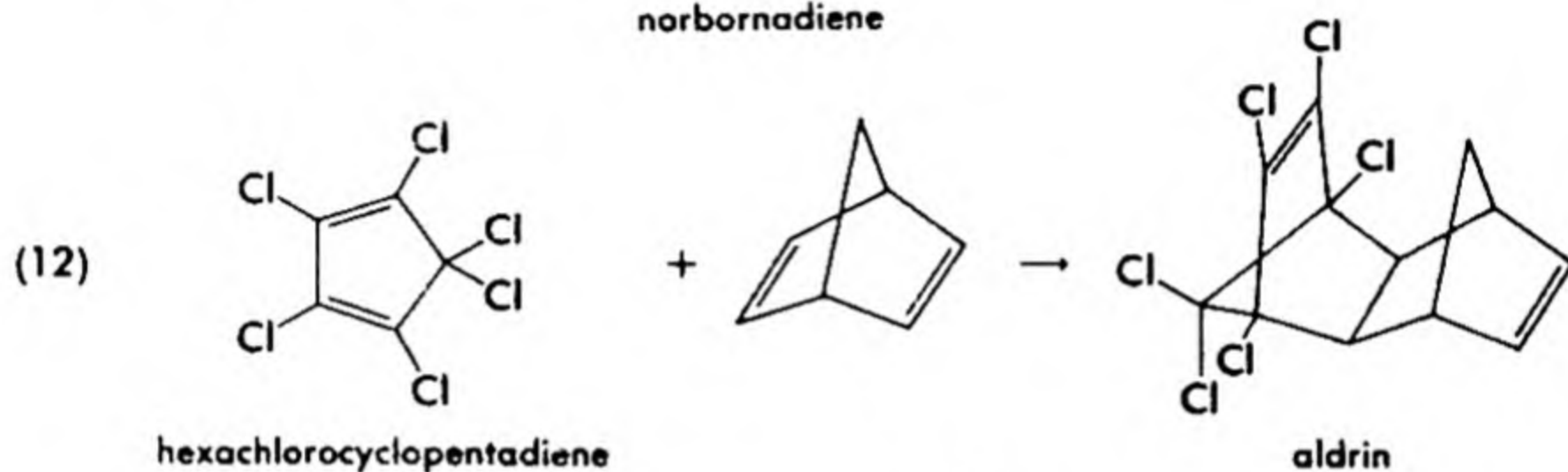
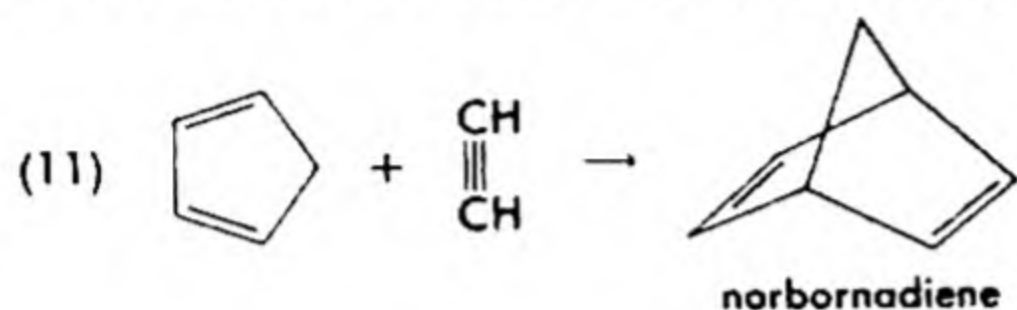
E. Typical Diels-Alder Reactions

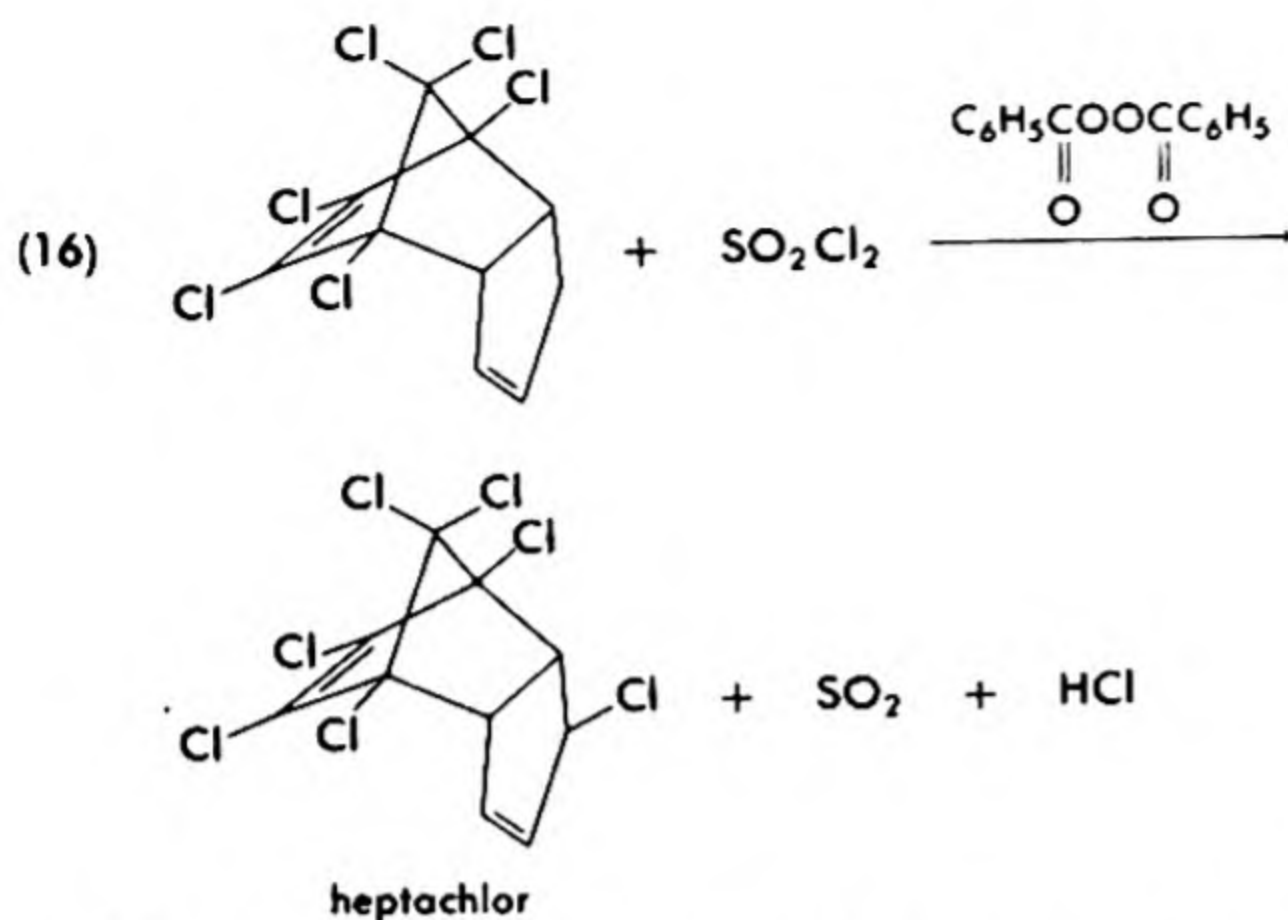
The scope of diene syntheses is so large that but a few of the more outstanding or more representative examples can be illustrated.

One of the oldest examples of a Diels-Alder reaction is the dimerization of cyclopentadiene. The monomer is unstable in respect to the dimer at normal atmospheric temperatures, but readily forms upon pyrolysis of the dimer at 170°. The dimer is called dicyclopentadiene.

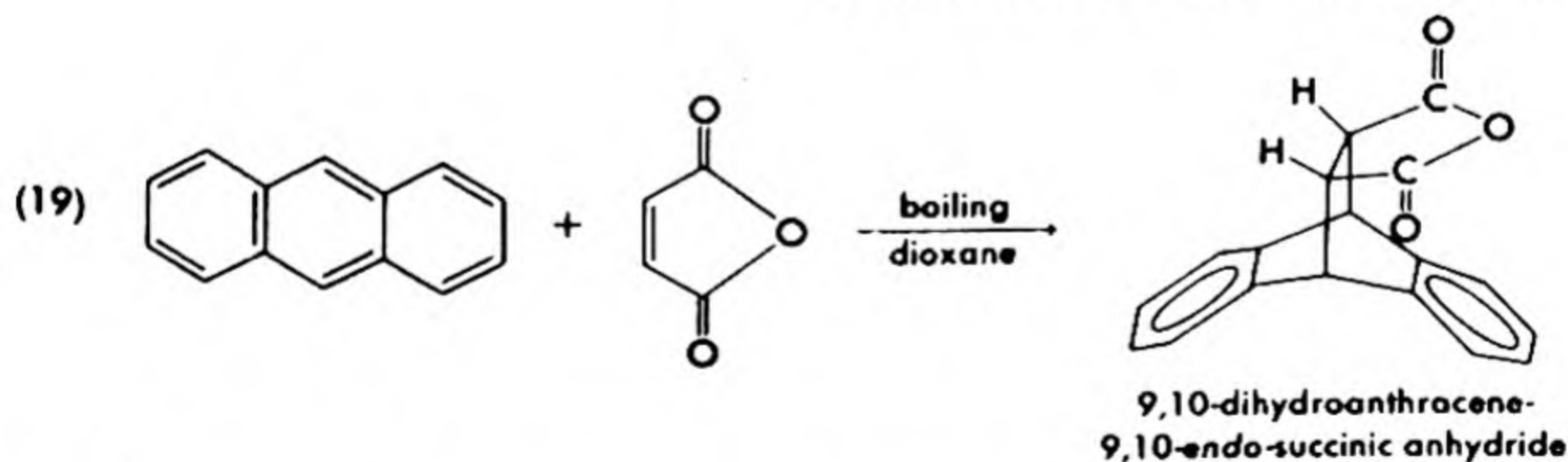
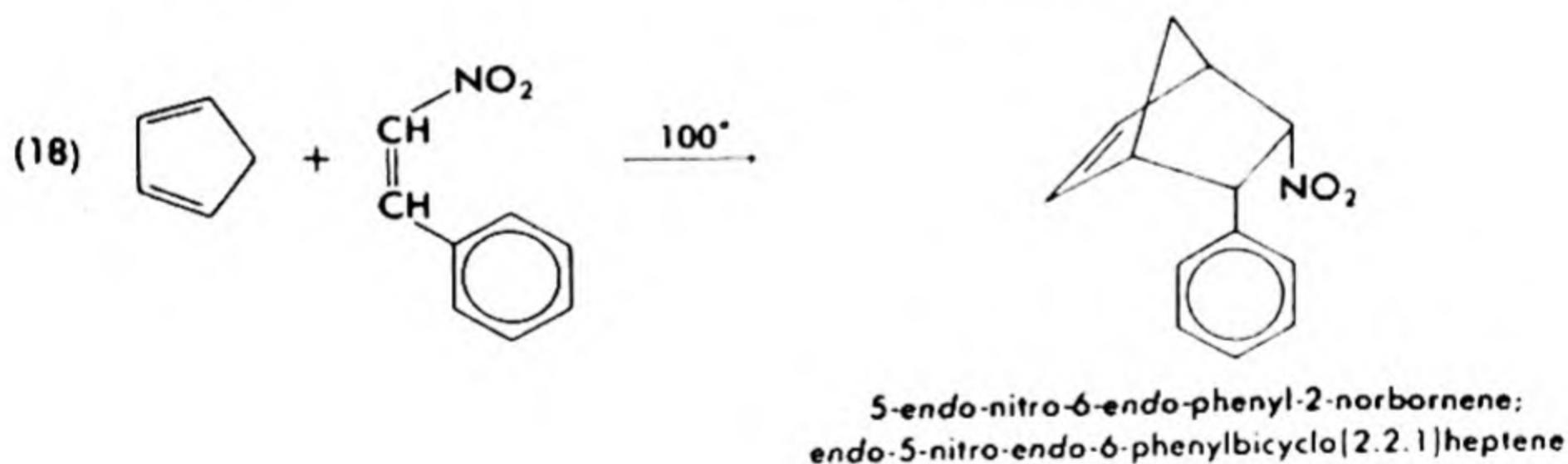
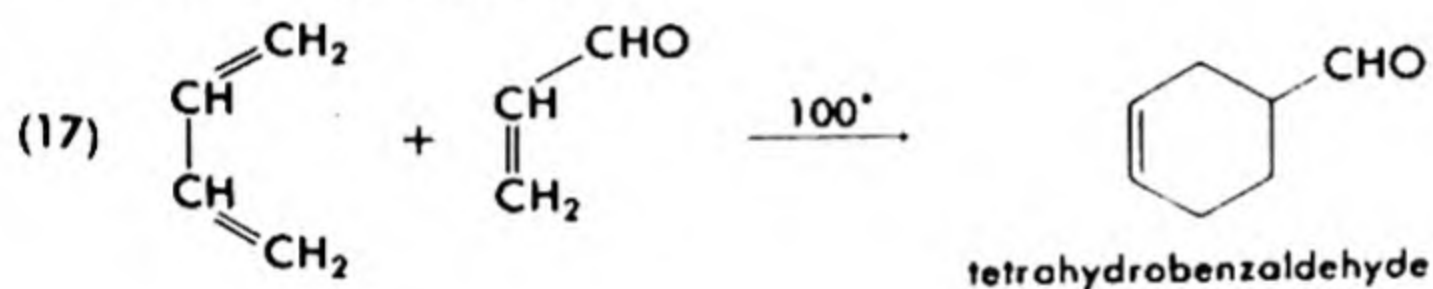


Similar diene syntheses are used to prepare a number of modern insecticides, aldrin, chlordan, dieldrin, and heptachlor. One may observe that two of these are named for the discoverers of the general reaction.





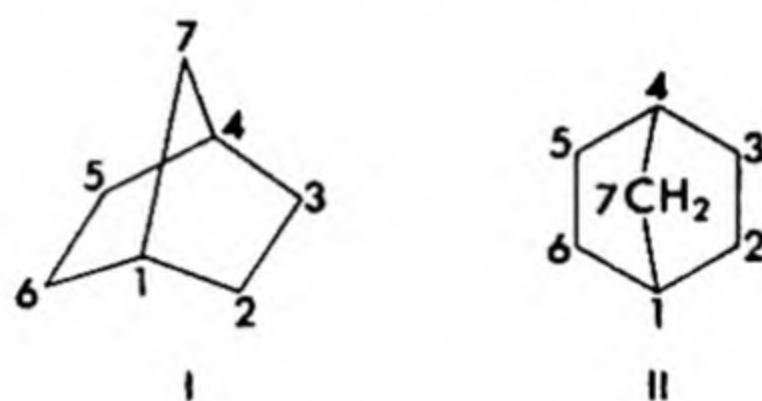
Other typical examples are the preparation of 1,2,3,6-tetrahydrobenzaldehyde, 5-*endo*-nitro-6-*endo*-phenyl-2-norbornene, and *cis*-9,10-dihydroanthracene-9,10-*endo*-succinic anhydride by the methods indicated in eqs. (17) through (19).



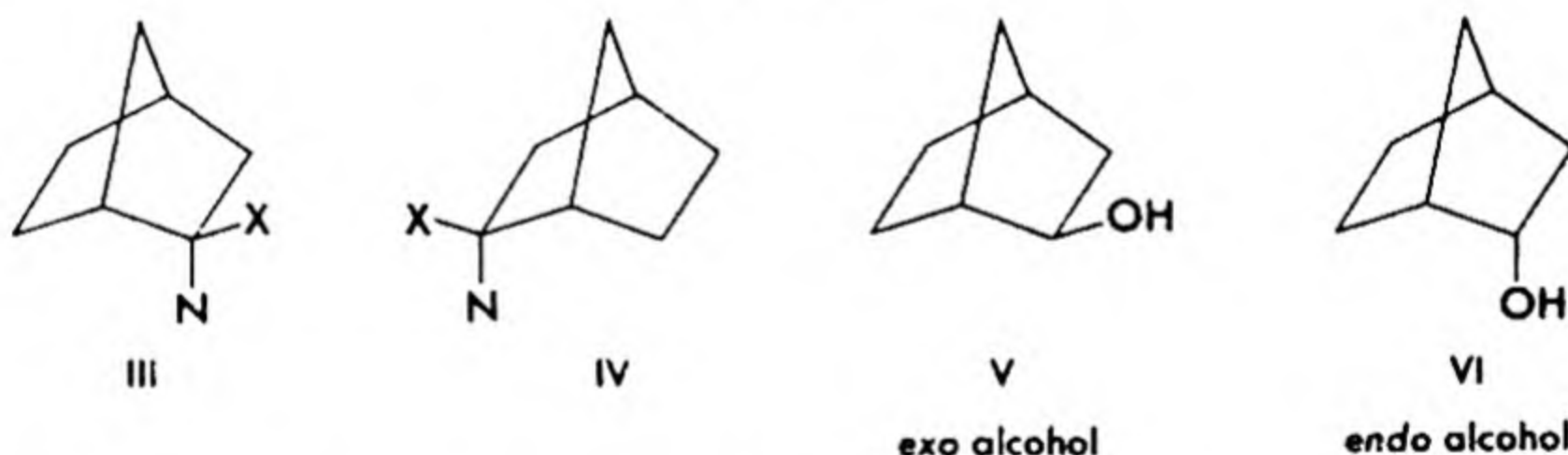
29-2 BRIDGED POLYCYCLIC COMPOUNDS

As noted above, Diels-Alder reactions of cyclic dienes offers ready synthetic routes to bridged compounds, that is, to compounds in which

two rings are joined together at two different carbon atoms. Such compounds have received considerable attention in recent years, both for theoretical studies and as useful materials and intermediates. In addition, many natural products contain bicycloheptane or bicyclooctane ring systems, and it is therefore worthwhile to review important points of isomerism, stereochemistry, and nomenclature of a few examples of bridged polycyclic compounds (fused aromatic ring systems have been treated elsewhere; see §5-1D). One of the most widely studied systems is the one available by Diels-Alder reactions of cyclopentadiene; the parent hydrocarbon with this ring system is called norbornane, I or II. Inspection of its formula shows that atoms 1 and 4 are bridged by two two-carbon bridges (atoms 2 and 3 and atoms 5 and 6) and by a single one-carbon bridge (atom 7). Thus atoms 1 and 4 are called "bridgehead" atoms. Two ways to represent norbornane are shown in I and II. Formula II is a pro-



norbornane

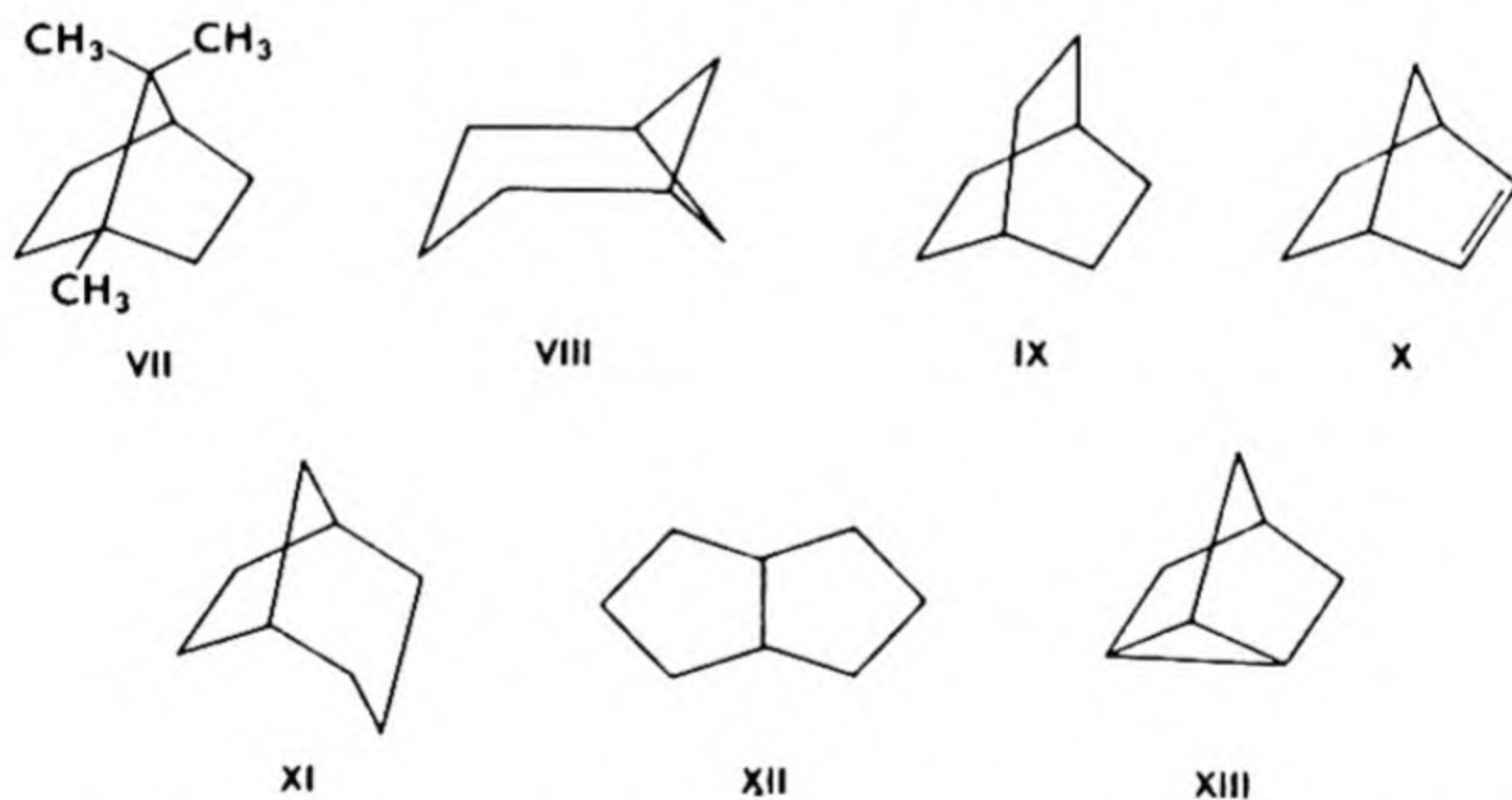


jection from directly above C_7 , while formula I is a projection looking from a little above the bridgehead of the molecule. As formulas of type I show stereochemistry considerably better than do those of type II, we shall generally use type I formulas.

Monosubstitution on norbornane at C_1 , C_4 , or C_7 does not lead to stereoisomers, but this is not the case with monosubstitution at C_2 (or the equivalent C_3 , C_5 , or C_6). Scrutiny of formulas III and IV indicates that the bonds represented by X and N are not identical. One, labeled X, is on the same side of the boat-form cyclohexane ring as the one-carbon bridge (C_7) and is termed "exo" and the other is on the opposite side and is called "endo." Thus V is *exo*-2-norbornyl alcohol and VI is *endo*-2-norbornyl alcohol. III is the mirror image of IV; hence each *endo* or *exo* isomer exists in D or L forms (i.e., "right-handed" and "left-handed" molecules).

Norbornane is so named because of its relationship to the terpene, bornane (see §41-1B), VII, to which it is related in being tris-demethylated. *Nor*-terpenes are completely demethylated terpenes. Such a method of nomenclature is useful only when a parent terpene is known, and general methods for naming have accordingly been devised. One of general use is to name one of the rings by a standard name and to name the third bridge as a substituent. A one-carbon bridge is termed "methano," a two-carbon bridge, "ethano," etc. Thus, norbornane, I, is called 1,4-methanocyclohexane, and the product of eq. (5) in §29-1D is called *endo*-1,4-methano-1,2,3,6-tetrahydrophthalic anhydride. The bridgehead carbon atoms are not necessarily the 1 and 4 atoms. Thus, an isomer of norbornane is VIII, 1,3-methanocyclohexane. Compound IX is called 1,4-ethanocyclohexane.

Another, more general, method of naming bridged compounds is the Baeyer system of nomenclature. In it, the root gives the number of carbon atoms in the combined ring systems, using IUPAC nomenclature, and the suffix indicates functional groups as is usual in IUPAC nomenclature. The term *cyclo* precedes the root, with bi, tri, etc., indicating the number of rings involved. Between *cyclo* and the root is a bracketed term with

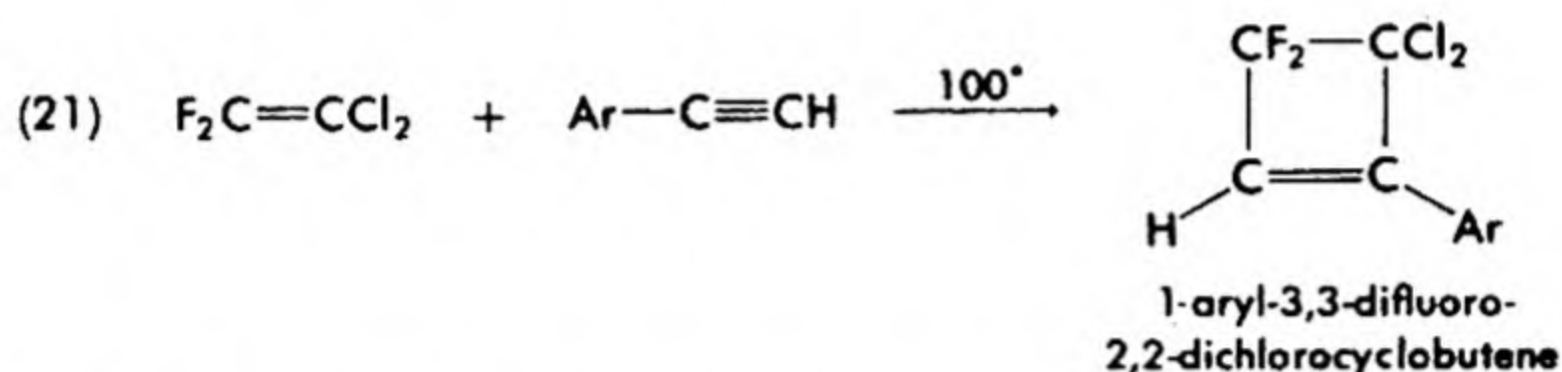
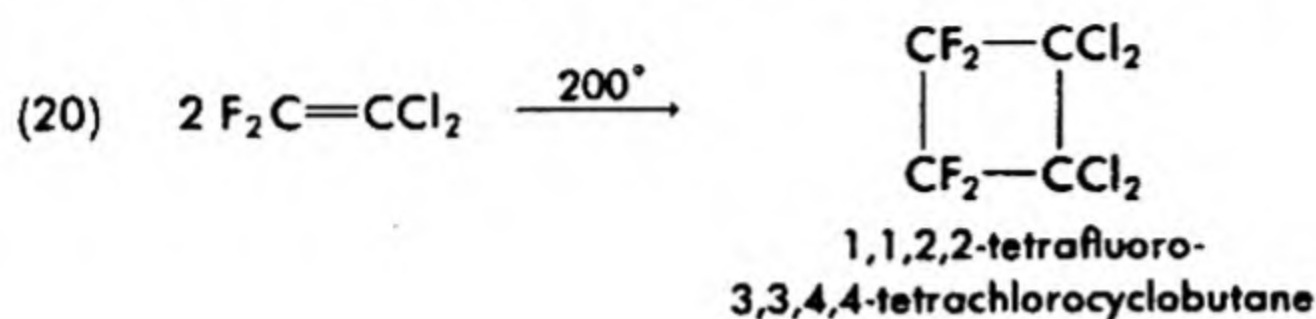


numbers indicating the number of atoms in each bridge lying *between* the bridgehead atoms. Thus, norbornane, I, is named bicyclo[2.2.1]heptane; V is *endo*-2-bicyclo[2.2.1]heptanol; norbornene, X, is 2-bicyclo[2.2.1]heptene, and VIII is bicyclo[3.1.1]heptane. IX is bicyclo[2.2.2]octane, while two of its structural isomers are bicyclo[3.2.1]octane, XI, and bicyclo[3.3.0]octane, XII. Compound XIII is a tricycloheptane.

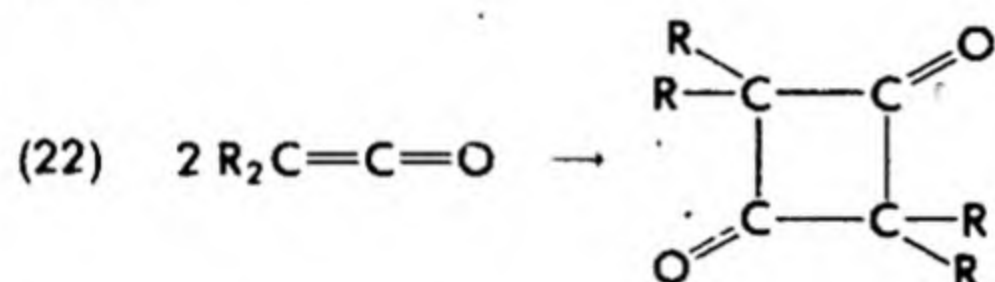
29-3 CYCLOBUTANE RING FORMATION

Derivatives of cyclobutane and cyclobutene can be prepared by addition of fluorinated olefins to themselves or to acetylenes in the presence of

polymerization inhibitors. Simple olefins do not add to each other in this manner (however, see the photochemical reactions, §26-9).



Self-additions of higher ketenes produce cyclobutanediones (whereas ketene itself forms a β -lactone, §18-3). The reaction occurs spontaneously at 20°



Like Diels-Alder reactions, these cyclobutane ring formations are cycloadditions in which the mode of electron shift is indeterminate. The necessity of polar groups would suggest electron-pair shifts, but no supporting evidence is available.

SUPPLEMENTARY READINGS

- Butz, L. W., and A. W. Rytina, "The Diels-Alder Reaction with Quinones and Other Cyclenones," *Org. Reactions*, **5**, 136-192 (1949).
 Holmes, H. L., "The Diels-Alder Reaction with Ethylenic and Acetylenic Dienophiles," *Org. Reactions*, **4**, 60-173 (1948).
 Kloetzel, M. C., "The Diels-Alder Reaction with Maleic Anhydride," *Org. Reactions*, **4**, 1-59 (1948).
 Martin, J. G., and R. K. Hill, "Stereochemistry of the Diels-Alder Reaction," *Chem. Rev.*, **61**, 537 (1961).
 Roberts, J. D., and C. M. Sharts, "Cyclobutane Derivatives from Thermal Cycloaddition Reactions," *Org. Reactions*, **12**, 1-56 (1962).

QUESTIONS AND PROBLEMS

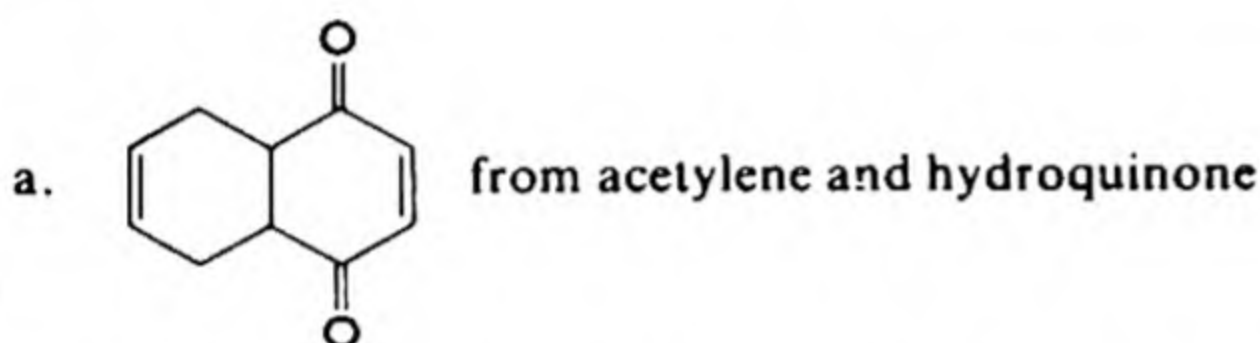
1. Give an explanation, illustration, or definition to show clearly what is meant by each of the following terms. Accompany diagrams with verbal explanation.

- | | |
|----------------------|----------------------------|
| a. dienophile | c. <i>exo-endo</i> isomers |
| b. bridgehead carbon | d. etheno bridge |

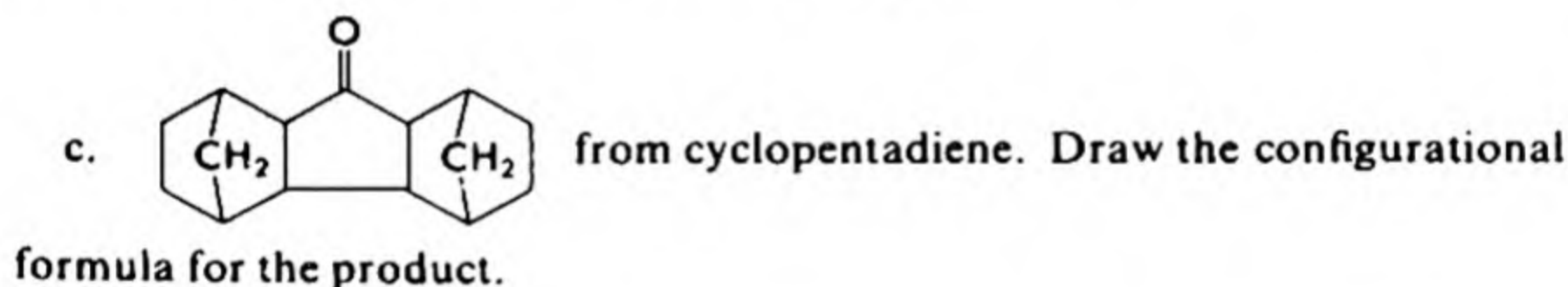
2. Write equations for the reactions that occur between the following reagents. Use structural formulas or ring symbols for organic compounds. Indicate essential special conditions.

- | | |
|--|---|
| a. methyl propiolate and butadiene | d. acrolein and 3-cyclohexylidene-1-propene |
| b. methyl fumarate and acetylene | |
| c. maleic anhydride and 1,1'-dicyclopentenyl | |

3. Show how the following compounds can be prepared from the indicated raw materials and inorganic reagents. Use structural formulas or ring symbols to represent organic compounds. Indicate necessary inorganic reagents and conditions.



b. 3-nitro-1,4-dimethylnaphthalene-2-carboxylic acid from tetramethylene dibromide, ethyl acetoacetate, and ethyl acrylate



UNIT III REVIEW PROBLEMS

1. Give an explanation, illustration, or definition to show clearly what is meant by each of the following terms. Diagrams and formulas should be accompanied with verbal explanation.

- | | |
|-----------------------------|----------------------------|
| a. activation energy | l. condensation reaction |
| b. active methylene group | m. conjugate acid |
| c. anionotropy | n. coupling |
| d. bond angle | o. covalent atomic radius |
| e. bond dissociation energy | p. detonation |
| f. Brønsted acid | q. diazotization |
| g. cationotropy | r. dienophile |
| h. chain propagation | s. electrophile |
| i. chain reaction | t. elimination reaction |
| j. chain transfer | u. <i>endo-exo</i> isomers |
| k. <i>cis-trans</i> isomers | v. exchange reaction |

w. explosion	an. nucleophile
x. free rotation	ao. organometallic compound
y. free radical	ap. <i>ortho-para</i> -directing group
z. Grignard reagent	aq. peroxidation
aa. hyperconjugation	ar. pi bond orbital
ab. inductive effect	as. polarizability
ac. inhibitor	at. polymerization
ad. initiator	au. reactive intermediate
ae. ionic mechanism	av. rearrangement reaction
af. labile group	aw. reductive alkylation
ag. lactam	ax. sigma bond orbital
ah. lactide	ay. solvolysis
ai. lactone	az. <i>syn-anti</i> isomers
aj. Lewis acid	ba. tautomerism
ak. mechanism	bb. transesterification
al. <i>meta</i> -directing group	bc. transition state
am. monomer	

2. Write the structural formula for an example of each of the following active intermediates and indicate the kind of reaction in which it participates.

- | | |
|-------------------------------|--------------------------------|
| a. anionic aryl sigma complex | e. carbonium ion |
| b. benzyne | f. carbonyl sigma complex |
| c. carbanion | g. cationic aryl sigma complex |
| d. carbene | h. free alkyl radical |

3. Write equations for reactions of actual compounds which illustrate the following named reactions. Use structural formulas for organic compounds. Indicate any necessary special conditions.

- | | |
|----------------------------------|------------------------------------|
| a. Arndt-Eistert reaction | s. Grignard reaction |
| b. Beckmann rearrangement | t. Hell-Volhard-Zelinsky reaction |
| c. Cannizzaro reaction | u. Hinsberg reaction |
| d. Claisen ester synthesis | v. Hofmann degradation |
| e. Claisen rearrangement | w. Hofmann rearrangement of amides |
| f. Clemmenson reduction | x. Hofmann synthesis of amines |
| g. Criegee reaction | y. Lossen rearrangement |
| h. Curtius rearrangement | z. Malaprade reaction |
| i. Diels-Alder reaction | aa. Meerwein-Ponndorf reaction |
| j. Dow process | ab. Oppenauer oxidation |
| k. Étard reaction | ac. Perkin condensation |
| l. Fischer-Tropsch reaction | ad. Reformatsky reaction |
| m. Friedel-Crafts reaction | ae. Reimer-Tiemann reaction |
| n. Fries rearrangement | af. Rosenmund reduction |
| o. Gabriel's synthesis | ag. Sandmeyer reaction |
| p. Gattermann aldehyde synthesis | ah. Schotten-Baumann reaction |
| q. Gattermann diazo reaction | ai. Stephen reduction |
| r. Gattermann-Koch reaction | aj. Tischchenko reaction |

- | | |
|-----------------------------------|-----------------------------|
| ak. Ullmann reaction | an. Wolff-Kishner reduction |
| al. Wagner-Meerwein rearrangement | ao. Wurtz reaction |
| am. Williamson synthesis | ap. Wurtz-Fittig reaction |

4. Show how the following compounds can be prepared beginning with carbon (coke or charcoal) as the only source of compounds of carbon. Indicate all necessary reagents and special conditions.

- | | |
|---------------------------|-----------------------------------|
| a. mesitylene | c. methyl cyclopropyl ketone |
| b. methylethylacetic acid | d. 3,4-diethyl-3,4-dimethylhexane |

5. Show how the following compounds can be synthesized using as raw materials methanol, ethanol, acetone, acetic acid, benzene, phthalic anhydride, naphthalene, and inorganic reagents, including CS_2 , CO_2 , HCN and their salts and derivatives containing only one carbon atom (e.g., urea, phosgene). Indicate the reagents and necessary special conditions. Use structural formulas for organic compounds.

- | | |
|--|--|
| a. chloranil | i. triethylene glycol di-2-ethylbutyrate |
| b. methyl 2,4-dichlorophenoxyacetate | j. nylon 66 |
| c. isopropyl <i>N</i> -(3-chlorophenyl)-carbamate | k. Orlon (polyacrylonitrile) |
| d. 1,1-bis(<i>p</i> -chlorophenyl)-2-nitropropane | l. Glyptal (polyester of phthalic anhydride and diethylene glycol) |
| e. halazone | m. <i>o</i> -tricresyl phosphate |
| f. merthiolate | n. di-2-ethylhexyl phthalate |
| g. 2- <i>n</i> -hexylresorcinol | o. triacetin (glycerol triacetate) |
| h. sulfaguanidine | p. butoxyethyl stearate (assume tristearin available) |

UNIT



Constitutive Physical Properties

30

Index of Refraction

30-1 THEORY OF REFRACTION OF LIGHT

As a light beam passes from one medium to another along the path AA in either direction (Fig. 30-1), it is bent at the surface SS , between the media. This is due to the difference in the velocity of light in the two media, and results in the relationship given in eq. (1) in which i is the angle the incident light beam makes with a line perpendicular to the surface, yz in Fig. 30-1, and r the angle the refracted beam makes to the perpendicular. The value, n , is a property of the lower medium called its *refractive index*, when the upper medium is a vacuum. This is the *standard*

$$(1) \quad n = \frac{\sin i}{\sin r}$$

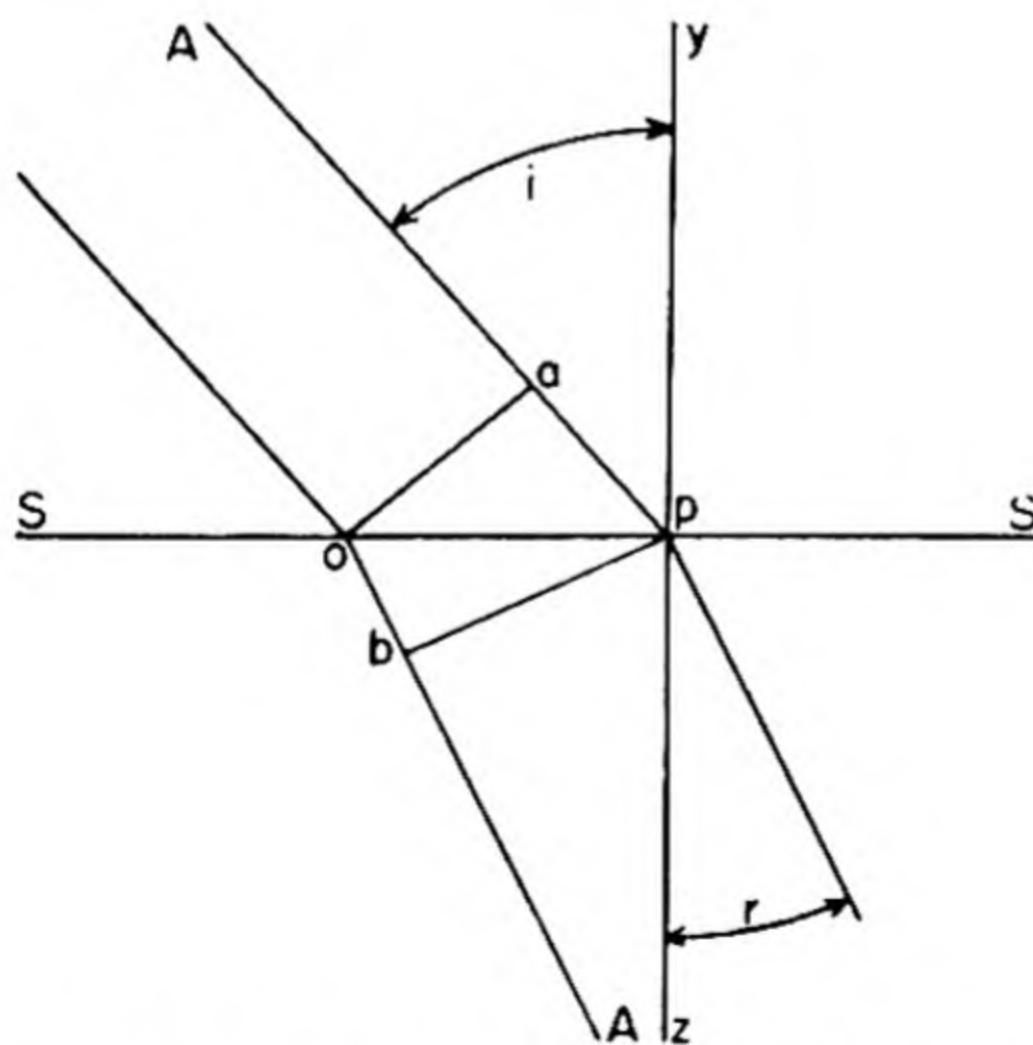


Fig. 30-1. Dependence of Angles of Incidence and Refraction on Velocities of Light in Two Different Media.

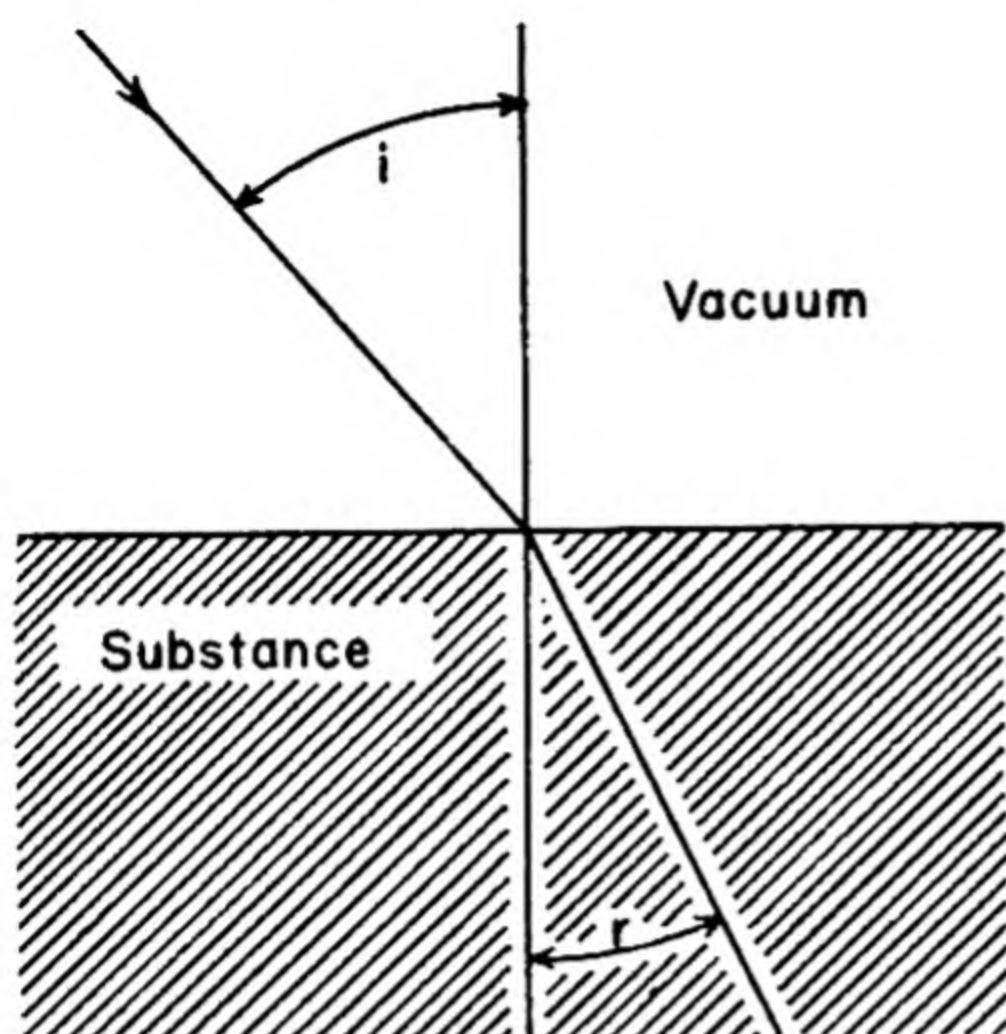


Fig. 30-2. Standard Refraction.

refraction (Fig. 30-2). In practice, however, the less dense medium is usually air. The observed refractive index may be corrected for this, if desired.

30-2 MEASURING REFRACTIVE INDEX

An instrument used to measure the index of refraction is called a refractometer. The two most common types of refractometers are the immersion refractometer (Fig. 30-3) and the Abbe refractometer (Fig. 30-4).

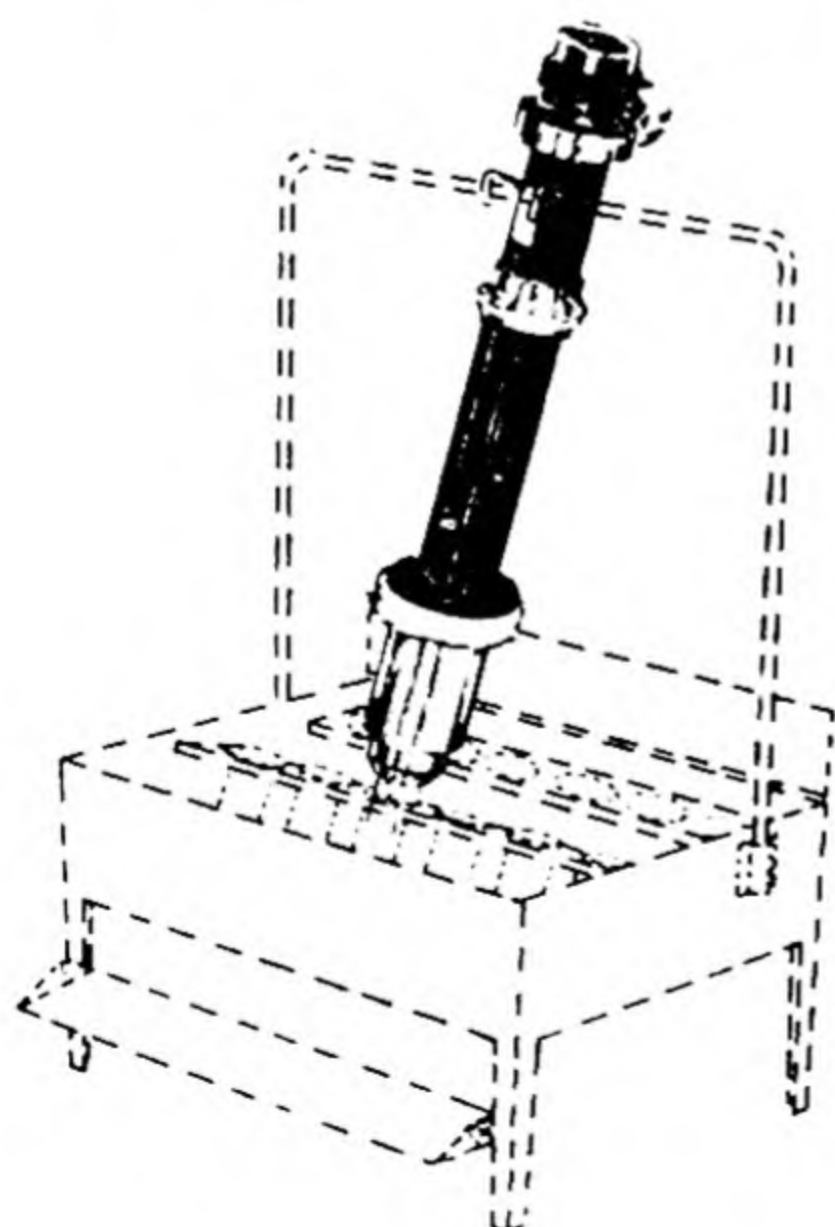


Fig. 30-3. Immersion Refractometer.

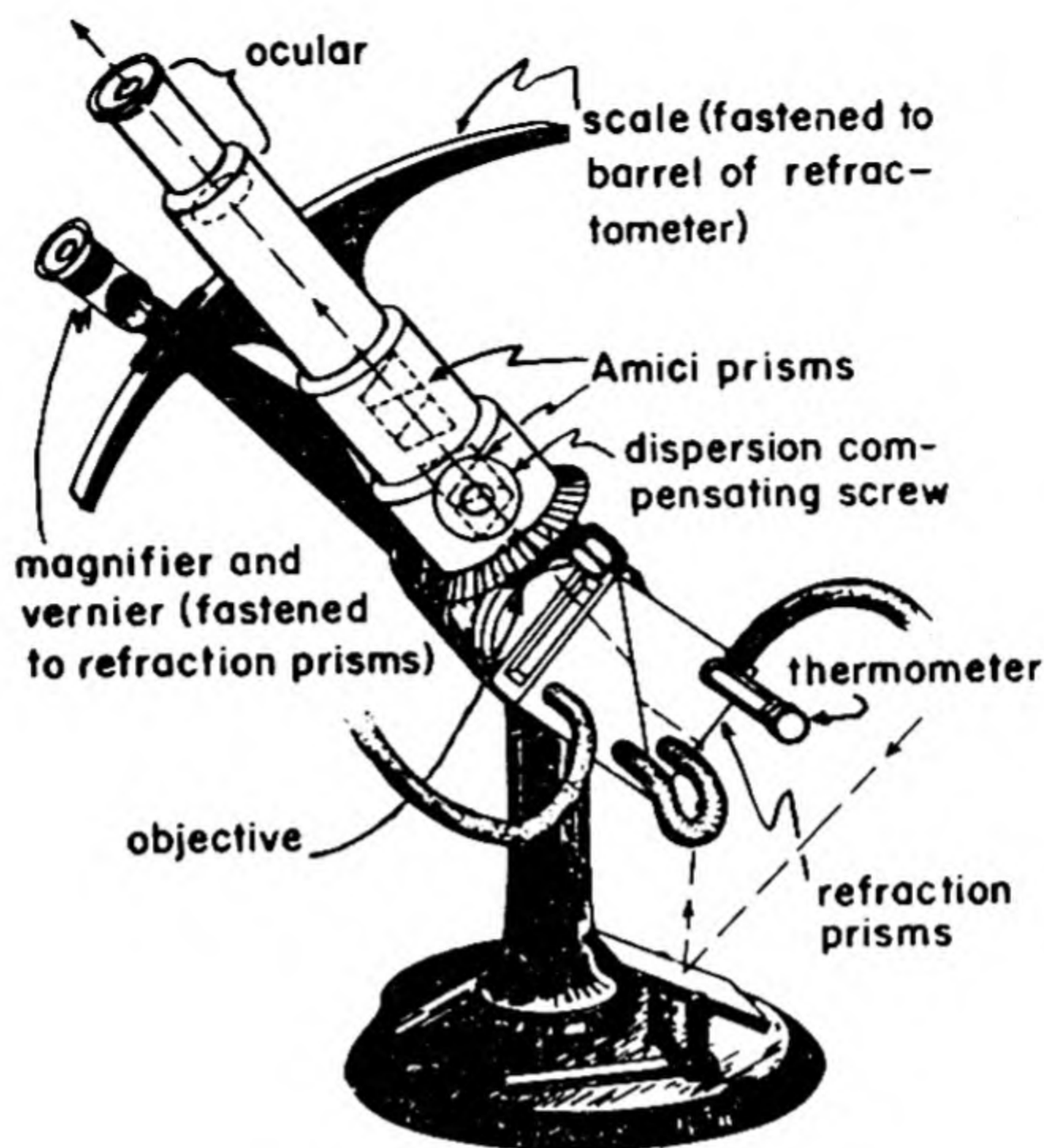


Fig. 30-4. Abbe Refractometer.

The Abbe refractometer requires but a drop or two of sample, which can be recovered if necessary, and has an almost foolproof means of obtaining and reading refractive indices. These features make it the most commonly used instrument for organic compounds, although it does not have quite the high accuracy of the immersion type, which requires a larger sample and somewhat more complex manipulation. The accuracy of the Abbe instrument is, nevertheless, much finer than that of any other simple tool for obtaining physical properties. With it, the refractive index can be read to an accuracy of about one part in ten thousand. The refractive index is marked directly on the scale of the Abbe instrument, which is possible since only one set of prisms is used with the Abbe refractometer. Refractive index varies with the wavelength of light, a property called *dispersion*. Recorded refractive indices are usually those at the D line of sodium, n_D .

30-3 USE OF REFRACTIVE INDEX

A. Common Use in the Laboratory

Like other physical constants, refractive index can be used in the identification of compounds. When used with melting point or boiling point, it

reduces the number of derivatives which need to be prepared for the identification of a compound, thus eliminating some of the tedium of the identification.

Another use of refractive index is the determination of purity of liquid samples. Liquids which have similar boiling points may have widely different refractive indices. Hence, index of refraction measurements serve as auxiliary means of following the purity of a product of distillation (Fig. 30-5).

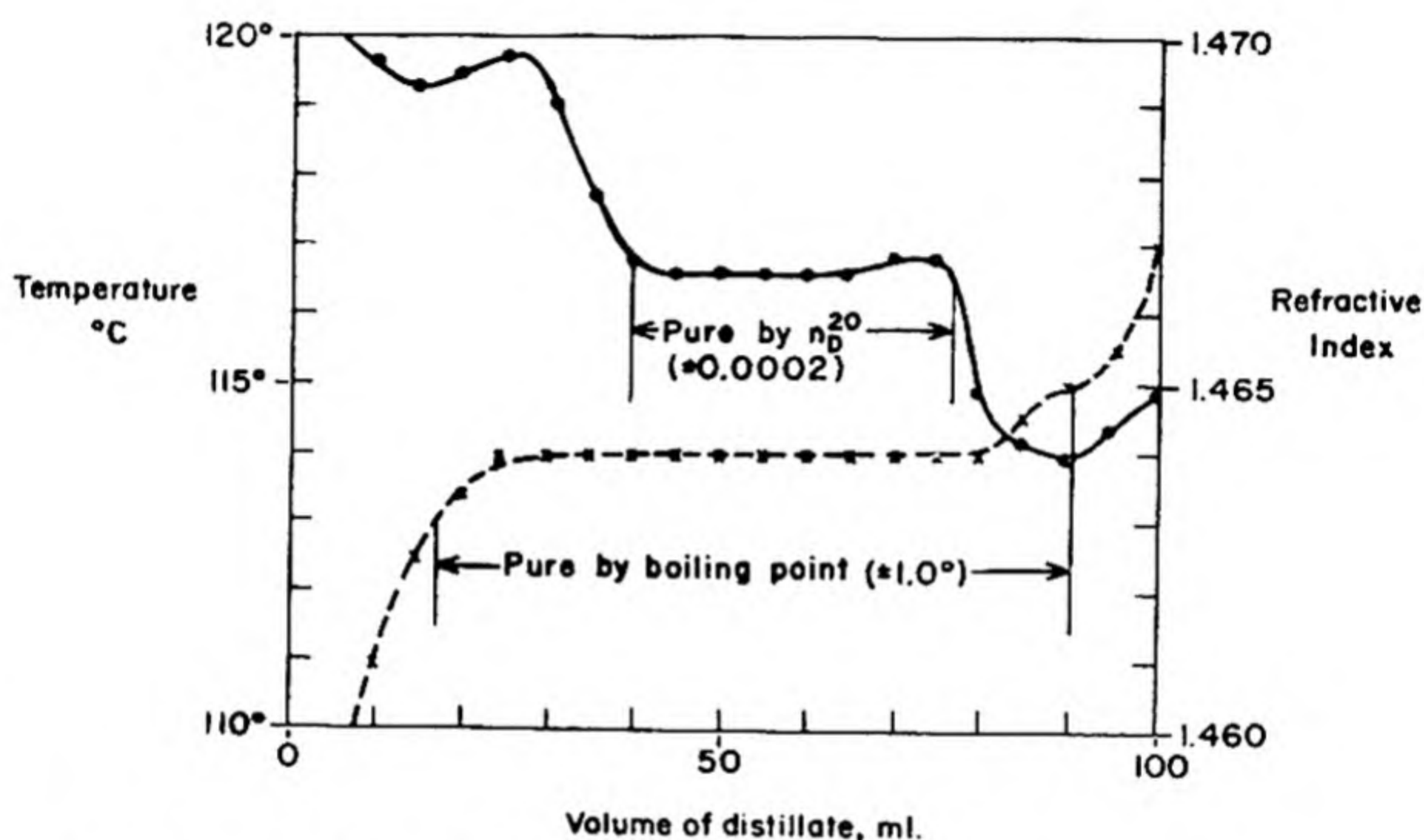


Fig. 30-5. Use of Refractive Index to Follow Purity of a Distillate.

B. Index of Refraction as a Constitutive Property

Since light velocity in matter depends on electron density and polarizability of electrons, change of refractive index with change in temperature or pressure for a given substance is actually closely related to change of density of the substance. Lorentz and Lorenz independently derived a function of refractive index, n , and density, d , at the same temperature, which is independent of temperature or pressure, and is called *specific refraction*, r .

$$(2) \quad r = \frac{n^2 - 1}{d(n^2 + 2)}$$

Observation that r varies regularly for homologous compounds led to the concept of molecular refraction, Mr , which is the specific refraction multiplied by the molecular weight, M . Calculation of Mr for some

TABLE 30-1. Molecular Refractions of Homologs.

Compound	n_D	Density	M_r	Difference
$n\text{-C}_5\text{H}_{12}$	1.3575	0.626	25.25	
$i\text{-C}_5\text{H}_{12}$	1.3537	0.620	25.25	
$n\text{-C}_6\text{H}_{14}$	1.3749	0.659	29.80	
$n\text{-C}_7\text{H}_{16}$	1.3876	0.684	34.50	
$n\text{-C}_8\text{H}_{18}$	1.3975	0.703	39.03	
CH_3OH	1.3288	0.791	8.11	
$\text{C}_2\text{H}_5\text{OH}$	1.3610	0.788	12.78	
$n\text{-C}_3\text{H}_7\text{OH}$	1.3854	0.804	17.54	
$i\text{-C}_3\text{H}_7\text{OH}$	1.3776	0.785	17.59	
$\text{CH}_2=\text{CH}(\text{CH}_2)_2\text{CH}_3$	1.3714	0.641	24.80	
$\text{CH}_2=\text{CH}(\text{CH}_2)_3\text{CH}_3$	1.3876	0.673	29.44	
$\text{CH}_2=\text{CH}(\text{CH}_2)_4\text{CH}_3$	1.3994	0.697	33.93	
$\text{CH}_2=\text{CH}(\text{CH}_2)_5\text{CH}_3$	1.4088	0.716	38.61	

alkanes, alcohols, and alkenes shows the results given in Table 30-1. The

$$(3) \quad M_r = \frac{M(n^2 - 1)}{d(n^2 + 2)}$$

facts that in such different series skeletal isomers should have almost the same molecular refraction and that the CH_2 increment should cause a nearly constant increment in molecular refraction suggest that molecular refraction must be additive as well as constitutive. Accordingly, atomic refractions have been computed by averaging atomic increments in a number of series. For example, the average difference in molecular refraction between RH and ROH is the atomic refraction for oxygen in hydroxy

TABLE 30-2. Atomic and Group Refractions.

Atom or Group	Refraction	Atom or Group	Refraction
H	1.100	Cl	5.967
C (single bonds)	2.418	Br	3.863
N (1° amino)	2.322	I	13.900
N (2° amino)	2.499	$\text{C}=\text{C}$ (isolated)	6.569
N (3° amino)	2.840	$\text{C}=\text{O}$ (isolated)	4.629
O (hydroxy)	1.525	$\text{C}\equiv\text{C}$	7.234
O (ether)	1.643	$\text{C}\equiv\text{N}$	5.459
F	1.090	$-\text{NO}_2$	6.52
S (mercapto)	7.69	S (sulfide)	7.77

groups. Some atomic refractions and group refractions are given in Table 30-2.

Since atomic refractions are frequently specific for given arrangements of atoms, for example, primary, secondary, and tertiary amines, the sum of atomic refractions for different arrangements can be compared with the molecular refraction calculated from experiment to act as a check on the proposed structure of a new compound.

SUPPLEMENTARY READING

Ingold, C. K., *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, New York, 1953, pp. 119-137.

QUESTION

1. Why is it not customary to correct index of refraction readings made in air to standard (vacuum) indices?

31

Optical Activity

31-1 POLARIZED LIGHT

A beam of ordinary light consists of a bundle of electromagnetic vibrations oriented in all possible directions about a line parallel to the path of the beam as an axis (Fig. 31-1). These vibrations, all added together, can be considered to behave as waves vibrating in two directions perpendicular to each other (Fig. 31-2).

While fluid substances and amorphous solids have the same refractive indices in all directions, this behavior is not the rule with crystalline solids. Only isometric solids have single refractive indices. Other crystalline solids are *birefringent*. Birefringence shows up as the giving of two images of an object refracted through the birefringent crystal (Fig. 31-3).

Light which passes through birefringent crystals has been broken down into perpendicular components, and the components separated from each other. Each image is borne by light vibrating in only one direction. Such light is called *plane-polarized* light. This can be demonstrated by placing

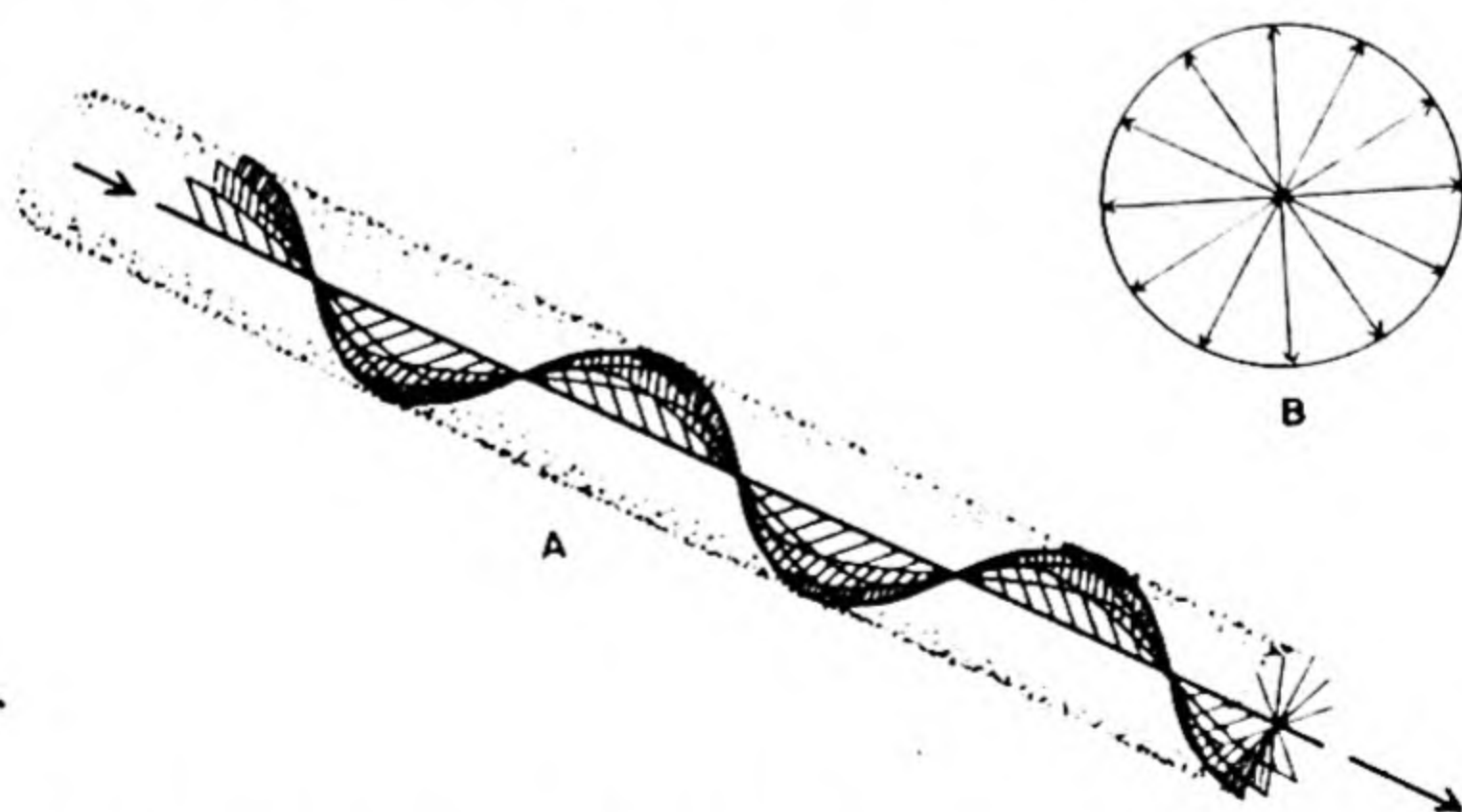


Fig. 31-1. Vibrations of Light Waves in a Beam of Light. (A) Some of the waves in a pencil of light, (B) End view of light beam, showing some vibration directions.

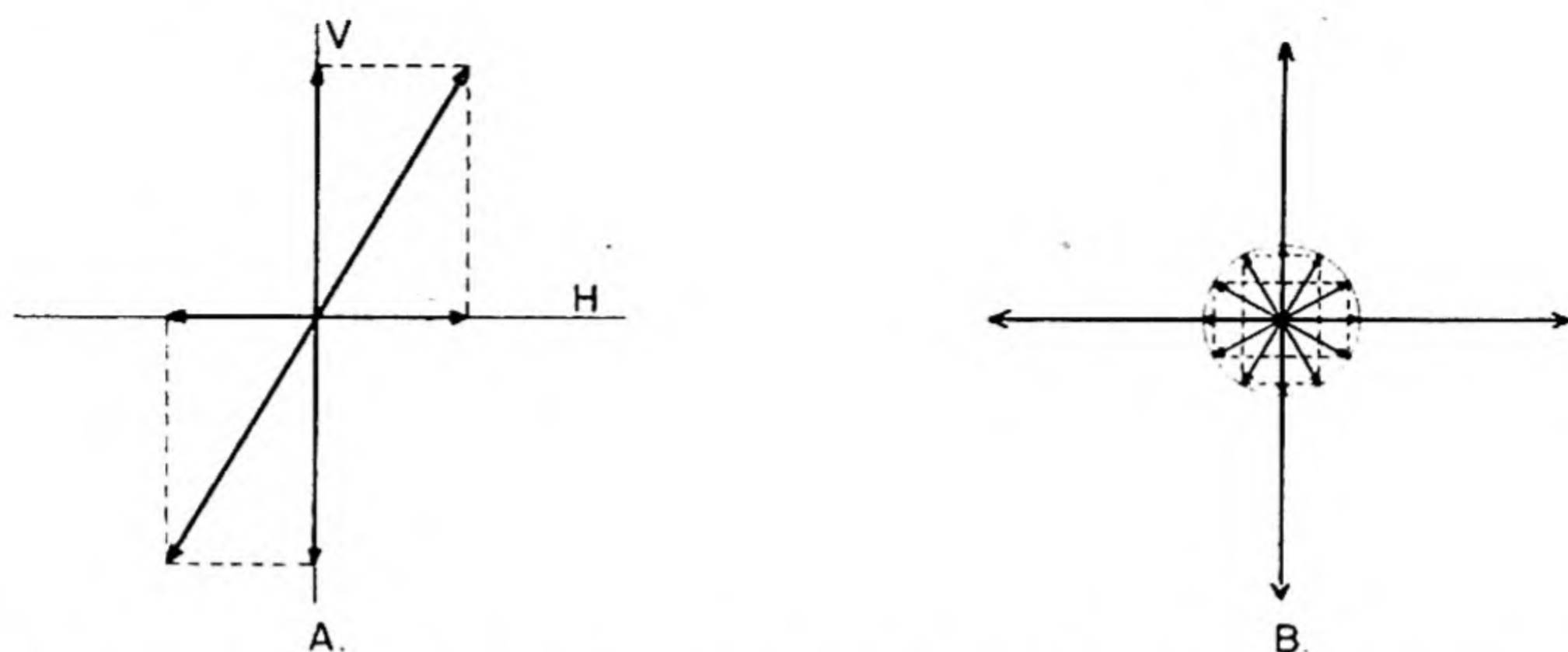


Fig. 31-2. Representation of a Light Wave as Perpendicular Vibrations. (A) Resolution of a vector into vertical and horizontal components, (B) Resolution of light waves into vertical and horizontal components.

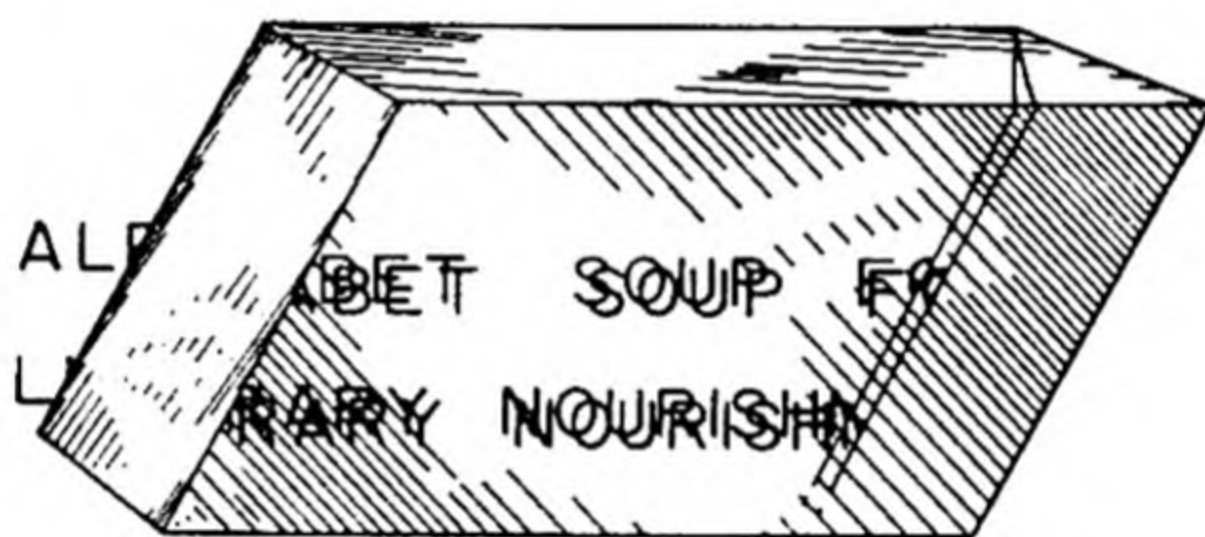


Fig. 31-3. Birefringence in Iceland Spar.

a *Polaroid* disc over the crystal and turning it about (Fig. 31-4). What happens is shown schematically in Fig. 31-5.

In an Iceland spar crystal which has been cut diagonally and cemented together again with Canada balsam, one of the two rays is totally reflected to the side, and only one polarized beam passes through. The elimination of the one ray depends on the critical angle between the spar and the balsam. A crystal so adapted is called a *Nicol prism*. It is a means of obtaining pure plane-polarized light.

A second Nicol prism placed after the first acts on the plane-polarized light in accord with the relative positions of the two prisms (Fig. 31-6). When prisms are parallel, the same component of the original light is acted upon in the same way; that is, all the plane-polarized light transmitted by the first prism is again transmitted by the second. When the prisms are crossed at 90° , however, the component transmitted by the first prism strikes the second in the position for complete reflection. None of the light is transmitted at all. Between these positions, the second Nicol

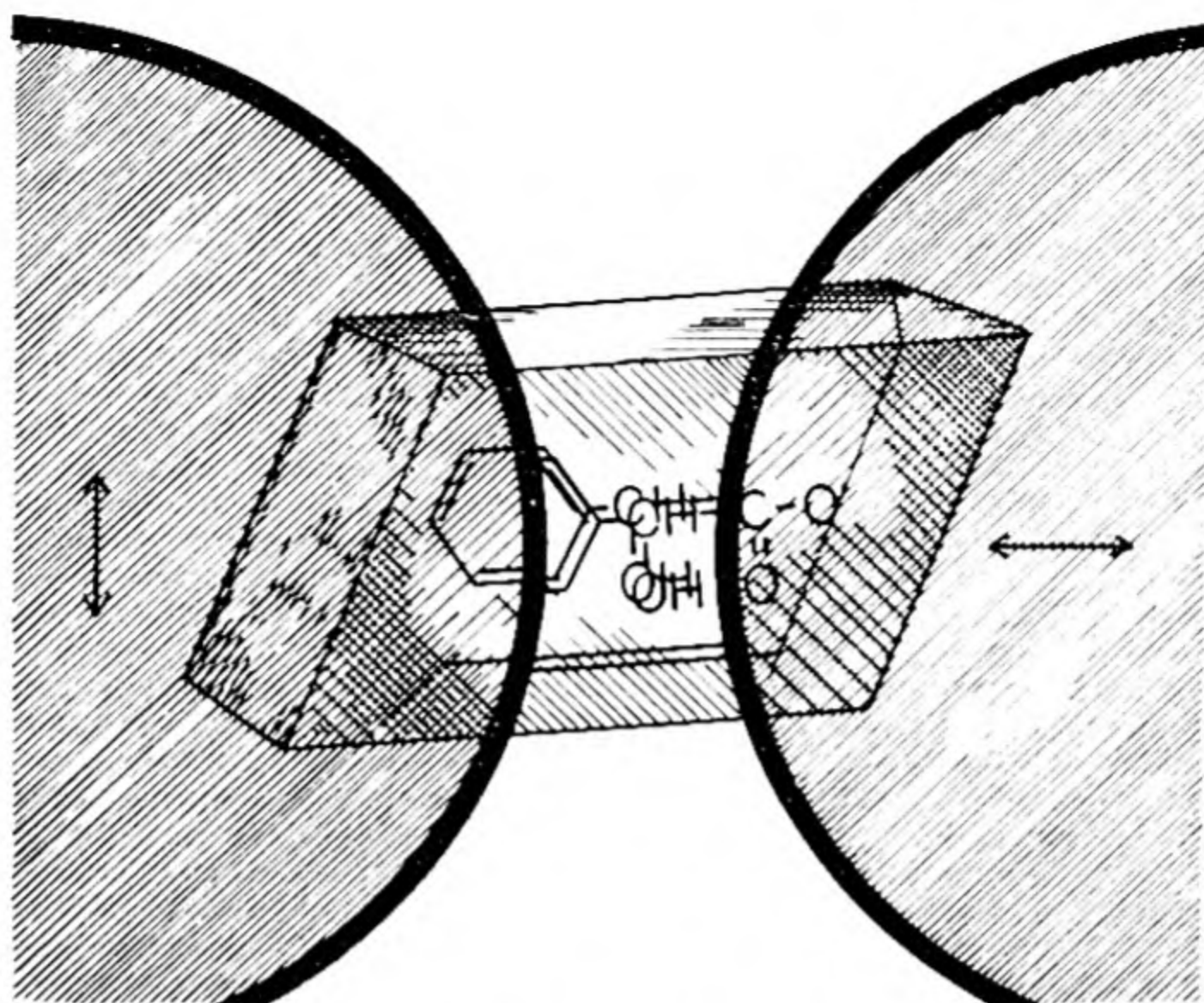


Fig. 31-4. Absorption of One of Two Images by Properly Placed Polaroid Discs.

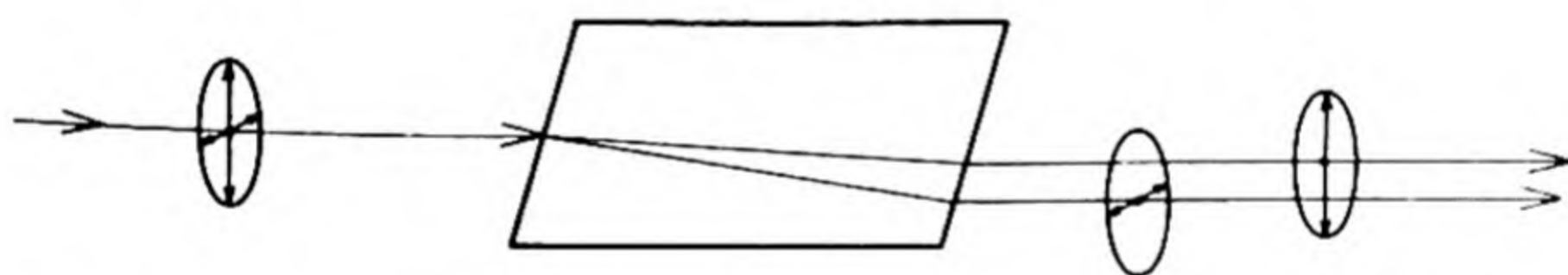


Fig. 31-5. Separation of Light into Polarized Beams by Birefringent Crystal.

prism resplits the plane-polarized light into new components (Fig. 31-2A), part of which is then reflected and part transmitted, so that the end view is darker than for parallel position, but not as black as for crossed position.

Thus, the second Nicol prism is able to establish the plane of polarized light in relationship to the first prism. It is accordingly called the analyzer. The first prism is called the polarizer. An instrument using this arrangement, plus a double 180° protractor which measures the angle of the analyzer from the crossed position, is called a *polariscope* or *polarimeter*.

31-2 OPTICALLY ACTIVE SUBSTANCES

When certain substances, such as crystalline quartz, are placed between the Nicol prisms of a polariscope, the relationship between the two prisms is changed in regard to the angles at which total extinction and complete transmission occur. The new positions for these effects show that the sub-

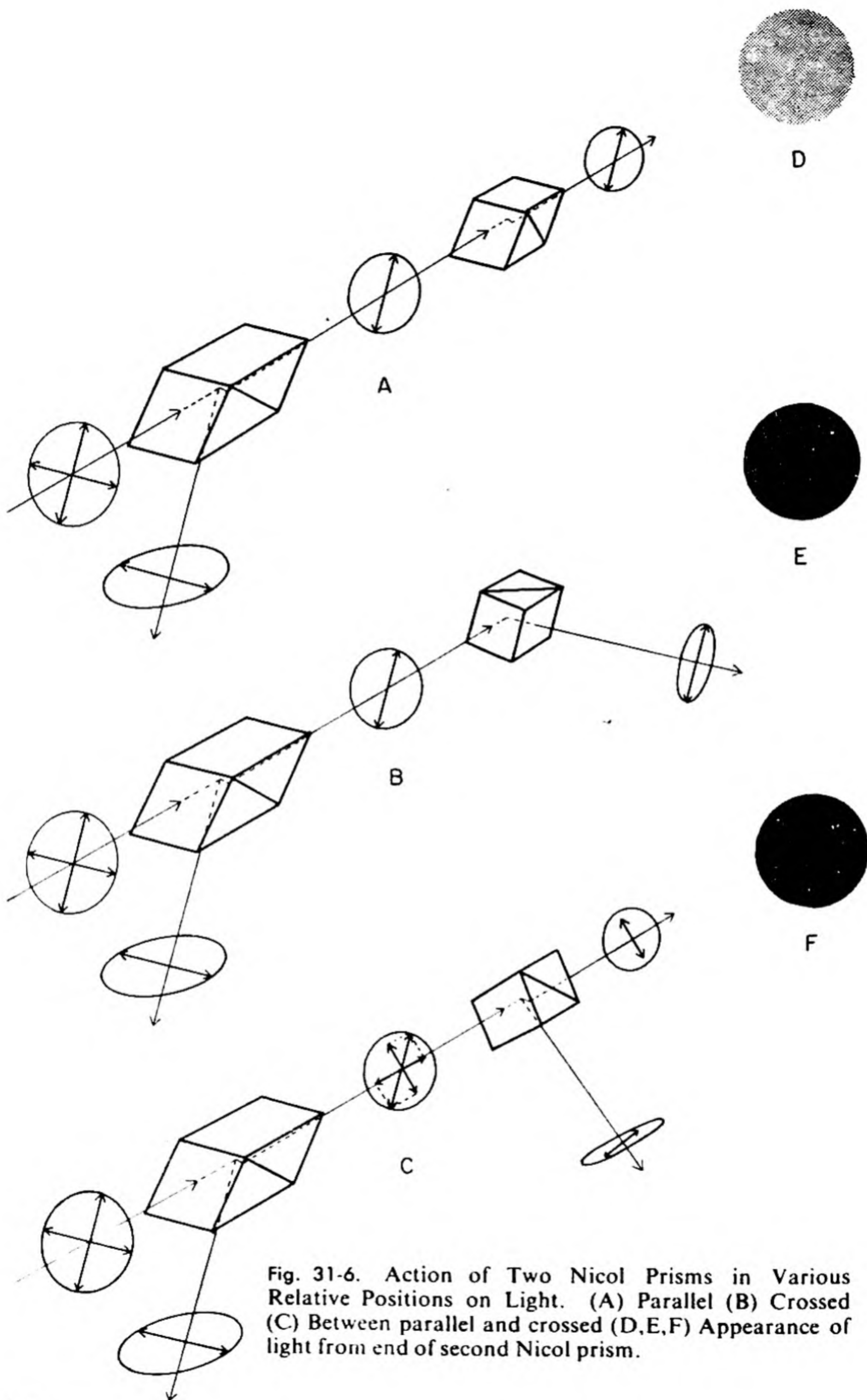


Fig. 31-6. Action of Two Nicol Prisms in Various Relative Positions on Light. (A) Parallel (B) Crossed (C) Between parallel and crossed (D,E,F) Appearance of light from end of second Nicol prism.

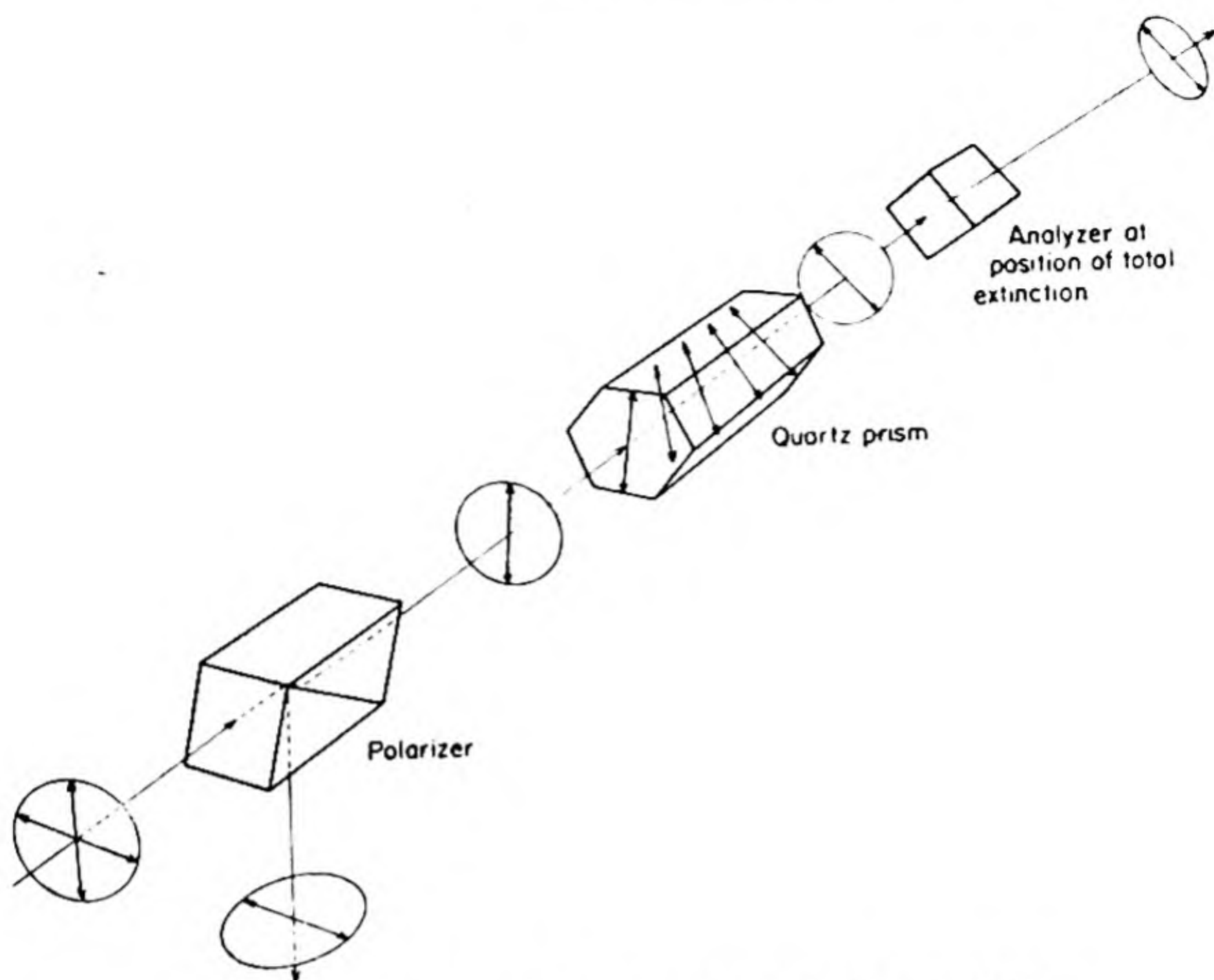


Fig. 31-7. Rotation of Plane-Polarized Light by Quartz Prism.

stance has twisted, or rotated, the plane of polarized light (Fig. 31-7). Substances which rotate plane-polarized light are said to be *optically active*.

Some optically active substances such as quartz lose this property upon being melted. Whatever is responsible for the property in quartz lies in the orderly arrangement of atoms in the crystal. On the other hand, many optically active substances, such as sucrose (cane sugar), maintain their activity in solution or in the liquid state.

31-3 MOLECULAR BASIS OF OPTICAL ACTIVITY

Louis Pasteur's observation that sodium ammonium tartrate has right- and left-handed crystals, or mirror image crystals, furnished an important clue to the molecular basis of optical activity. It was soon realized that molecules or ions of compounds that have optical activity in a fluid state are not identical with their mirror images—that is, they are *asymmetric*.

Asymmetry depends, in many carbon compounds, on the tetrahedral arrangement of four unlike groups about the same carbon atom (Fig.

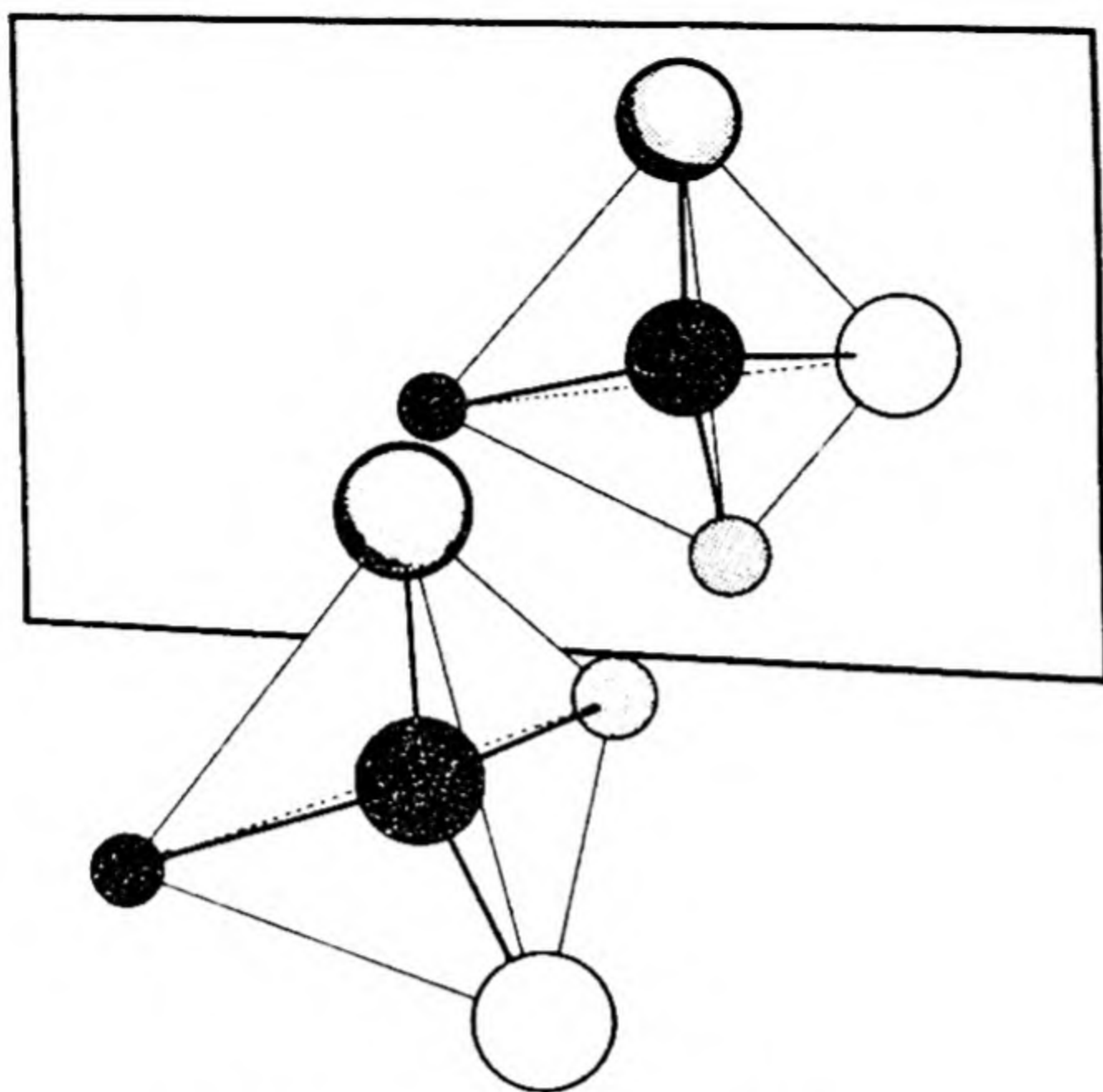


Fig. 31-8. Dissimilar Mirror Image.

31-8). Such a carbon atom is called an *asymmetric carbon atom*, often represented as C^* , whether the molecule as a whole is asymmetric or not. Carbon atoms which have two or more like substituents cannot be asym-

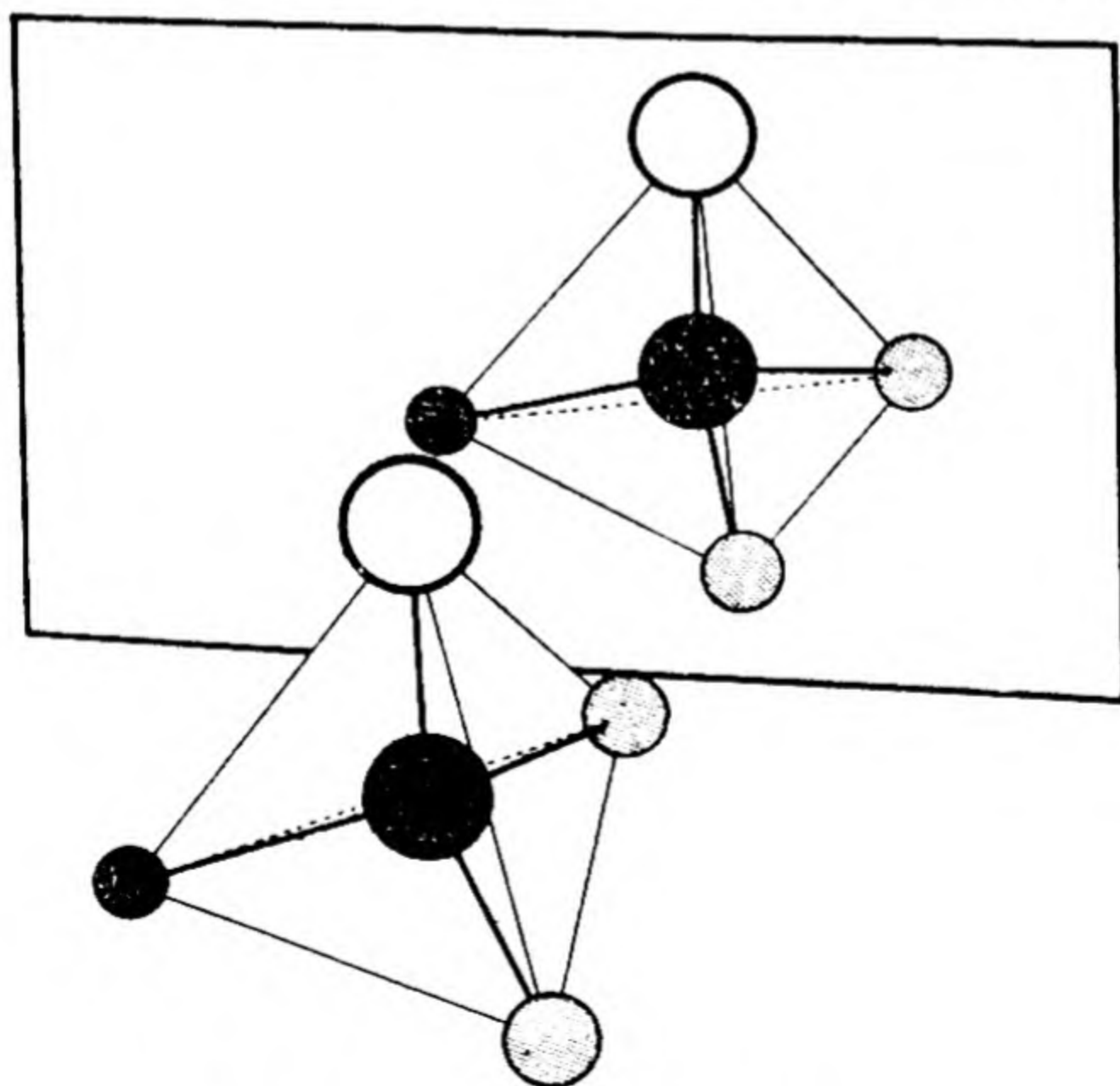


Fig. 31-9. Identical Mirror Image.

metric (Fig. 31-9). Compounds the molecules of which are structurally the same but differ in their effects on plane-polarized light are *optical isomers*. Isomers the molecules of which are mirror images of each other are called *enantiomorphs* (Gk., *enantios*, opposite, and *morphos*, shape). Asymmetric molecules have no plane of symmetry (Fig. 31-10).

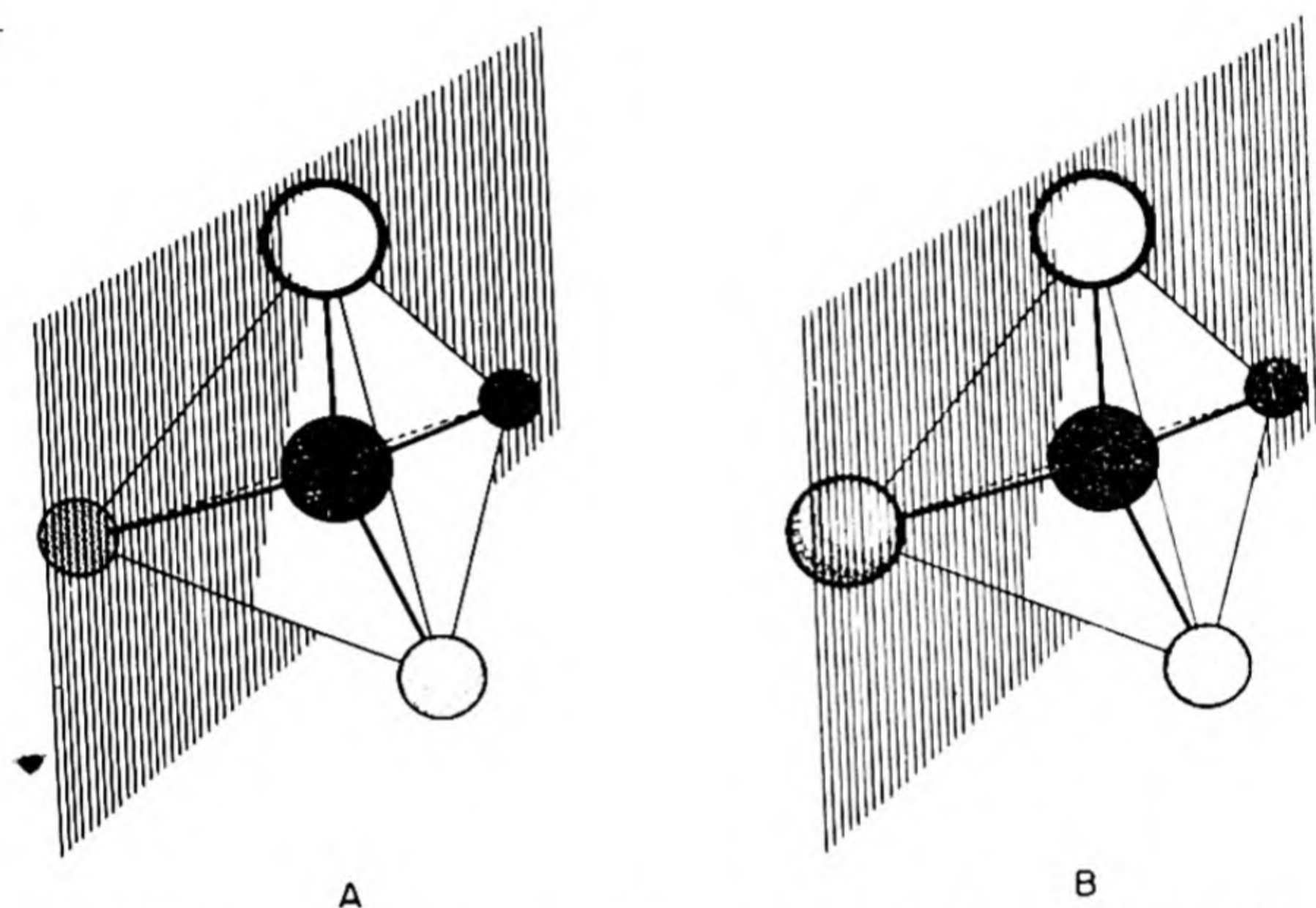


Fig. 31-10. Planes of Symmetry. (A) Molecule with plane of symmetry. (B) Molecule without plane of symmetry.

31-4 CONVENTIONS FOR CONFIGURATIONAL FORMULAS

Since optical activity depends on three-dimensional geometry, a simple structural formula written on a two-dimensional space is inadequate to represent an asymmetric molecule. Arbitrary conventions are used to represent optical isomers by two-dimensional formulas without the necessity of drawing pictures of tetrahedra.

The plane formula represents a projection of a three-dimensional molecule (Fig. 31-11). For the formula to represent a unique configuration, it is necessary to fix the relative position of the molecule to the plane; otherwise, a projection might represent either of two enantiomorphs (Fig. 31-11 B or C). Let us say, then, that the projection must represent the molecule when the vertical edge of the tetrahedron is away from the observer, the horizontal edge toward the observer (Fig. 3-11A, B).

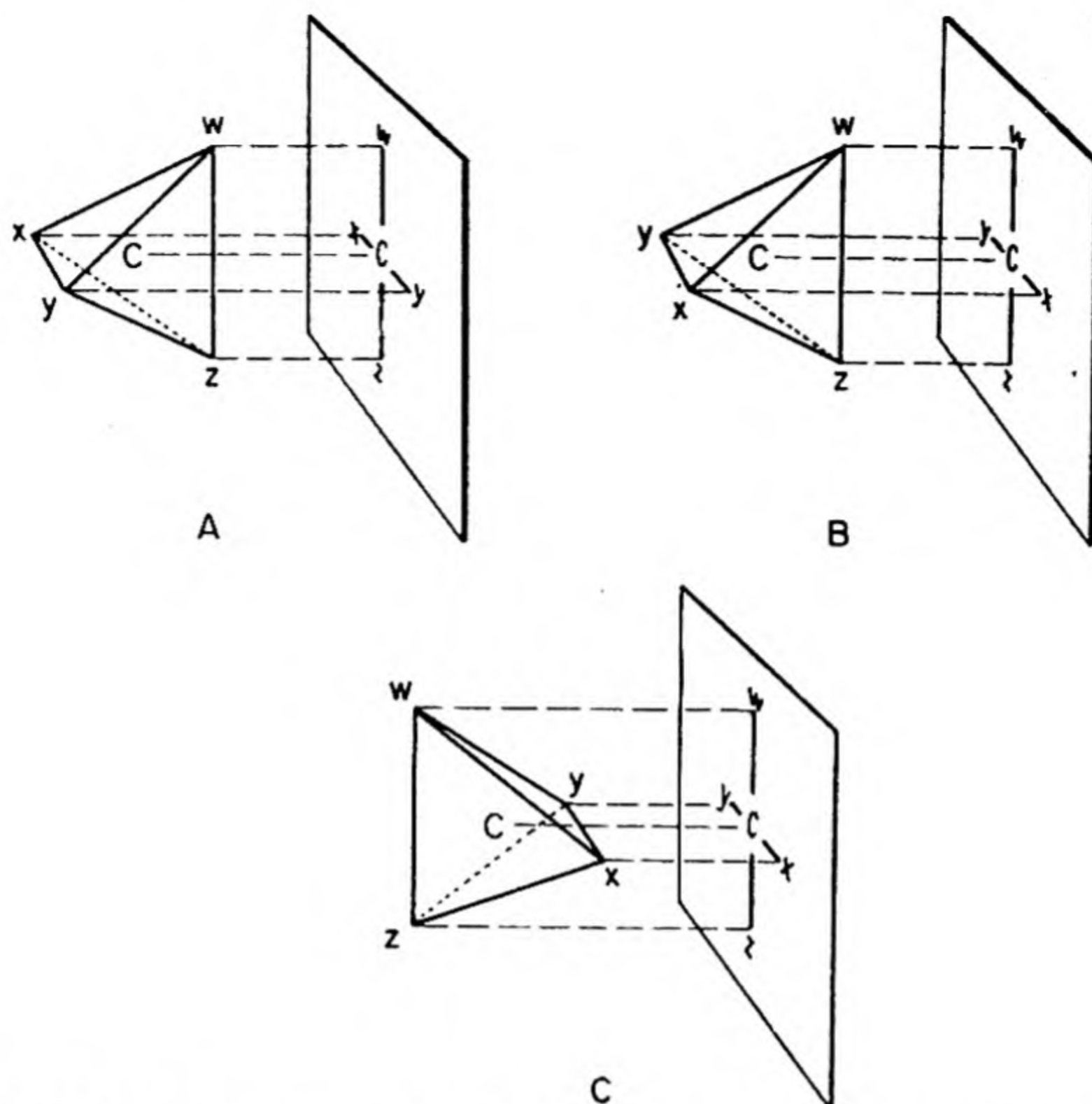


Fig. 31-11. Projections of Molecules onto Plane Surfaces. (B) Projection of mirror image of A, (C) Projection of A turned around.

It can be shown that certain transformations are allowable in a formula without change in the configuration of the molecule it represents. Molecular models should be constructed to establish the relationships. One permissible transformation and one forbidden by the convention are illustrated in Fig. 31-12 B and A, respectively.

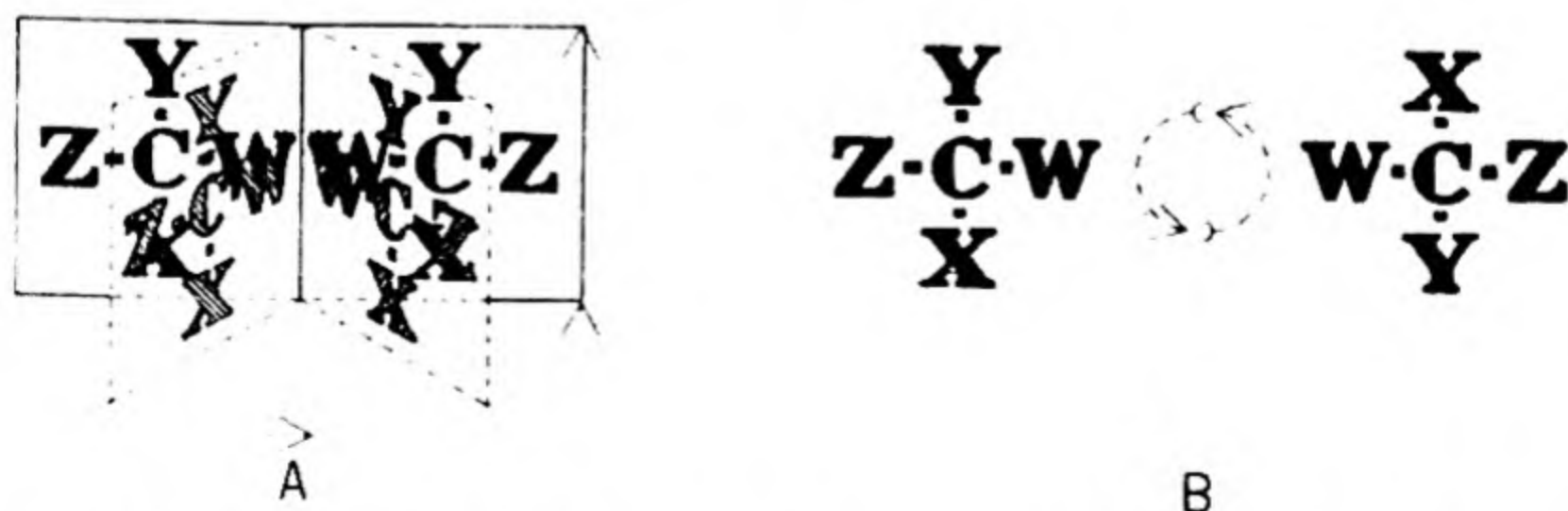
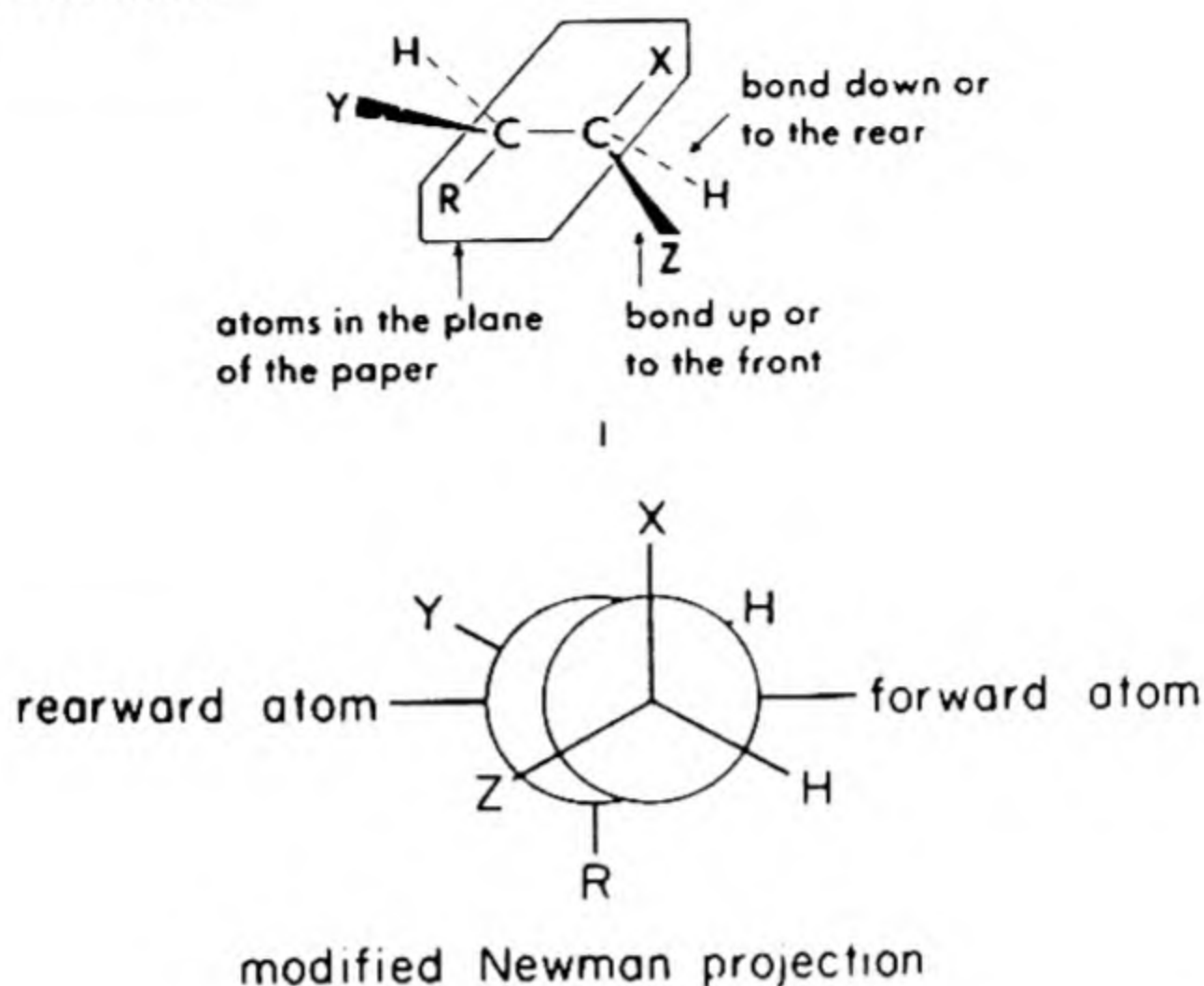


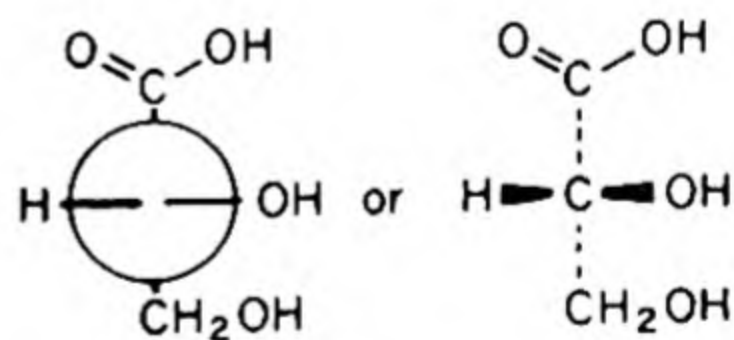
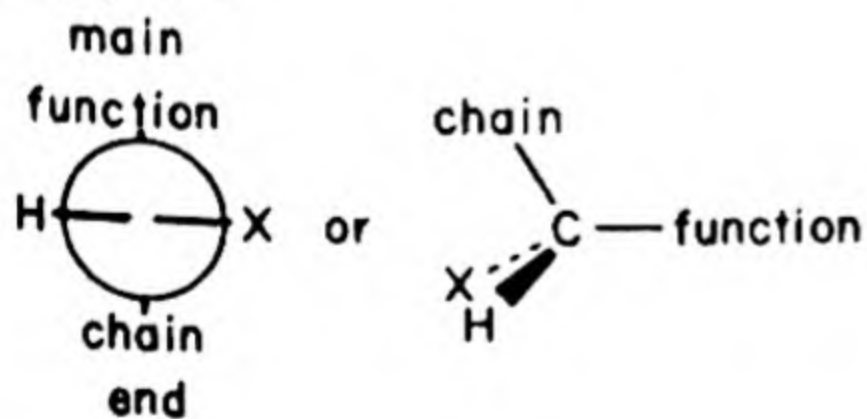
Fig. 31-12. Formalized Transformations in Configurational Formulas. (A) Forbidden folding of formula out of the plane on which the formula is written, (B) Permitted rotation of molecule 180° in plane of paper. (Rotation of 90° is also forbidden; see Fig. 31-11.)

Chemists are making increasing use of projection formulas, I or II, to represent molecules. This is much more satisfactory than the use of many artificial conventions.

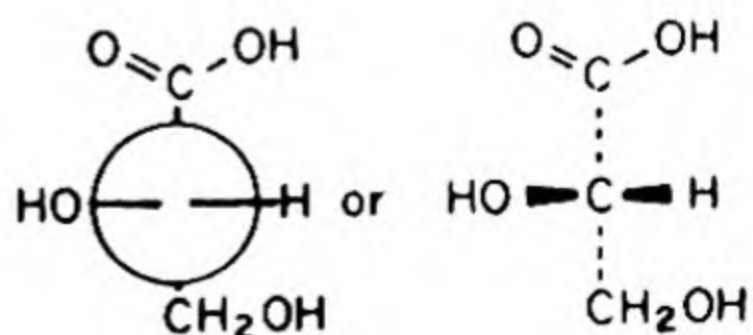
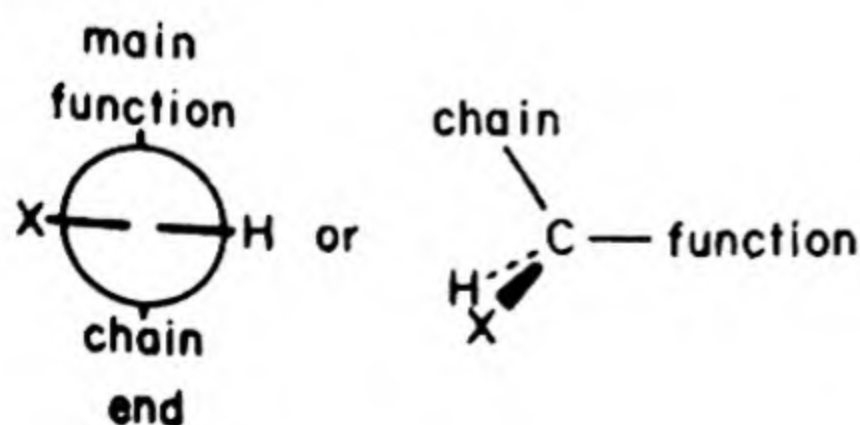


Various configurations have received names based on the names of the simple sugars (§38-1B(7)) which have related configurations. (See the formulas and terms given on the following pages.) Thus, *erythro* configurations have groups in the same relative positions as those in the sugar erythrose; *threo* configurations, those in the same relative positions as groups in threose, etc. Configurations other than the D- and L-glycero have more than one asymmetric center (discussion of which follows in the next section).

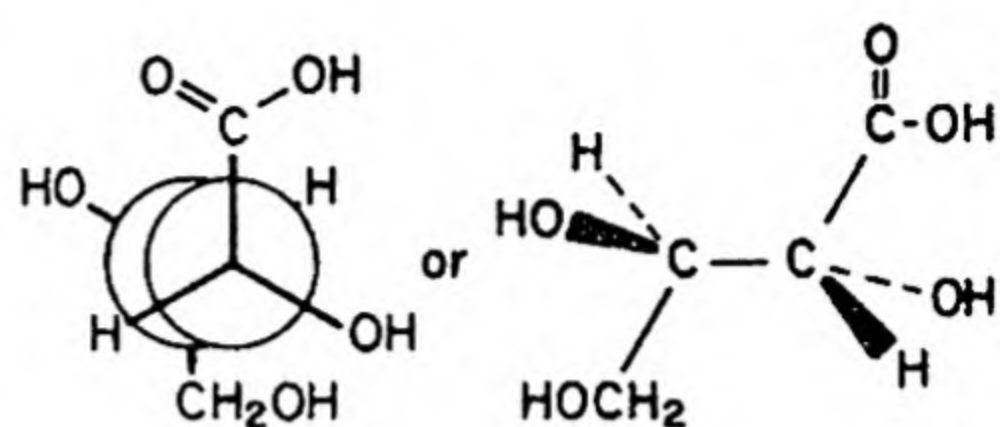
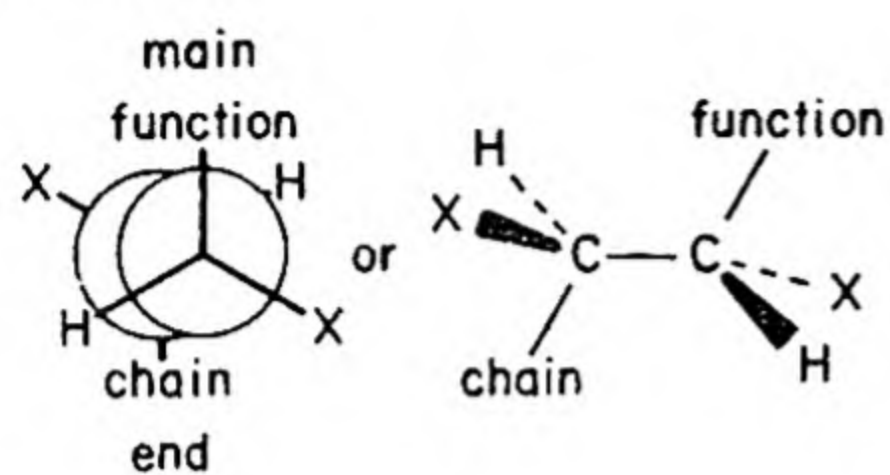
D-glycero:



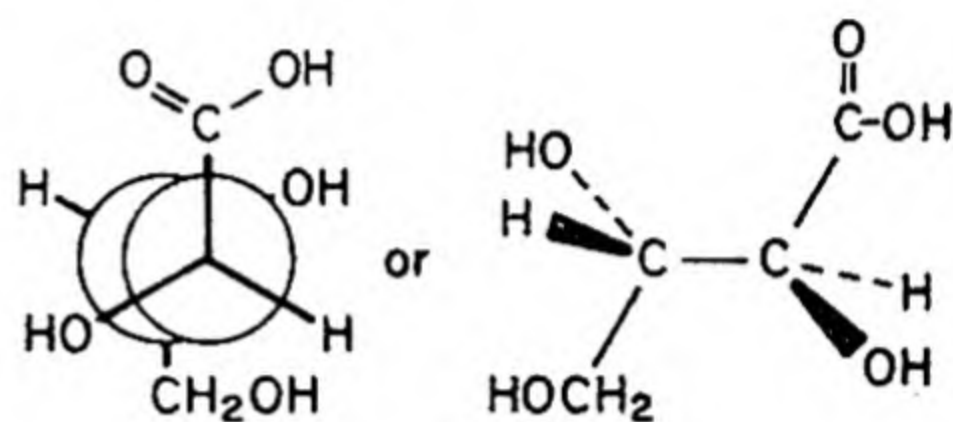
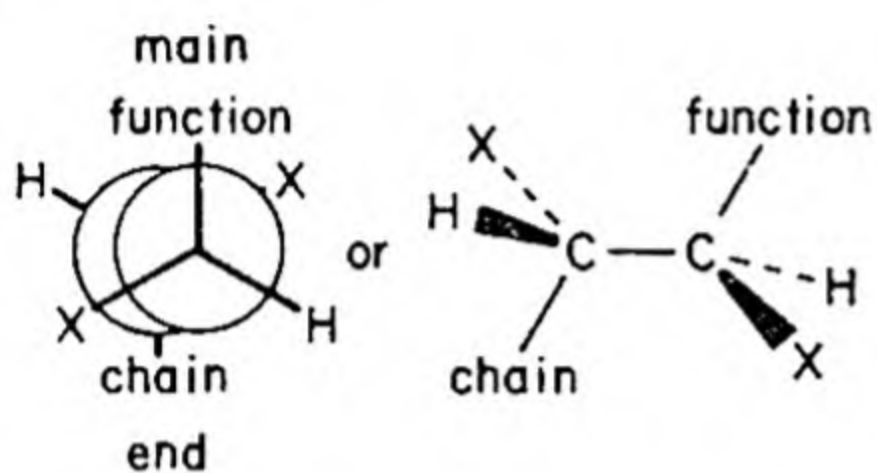
L-glycero:



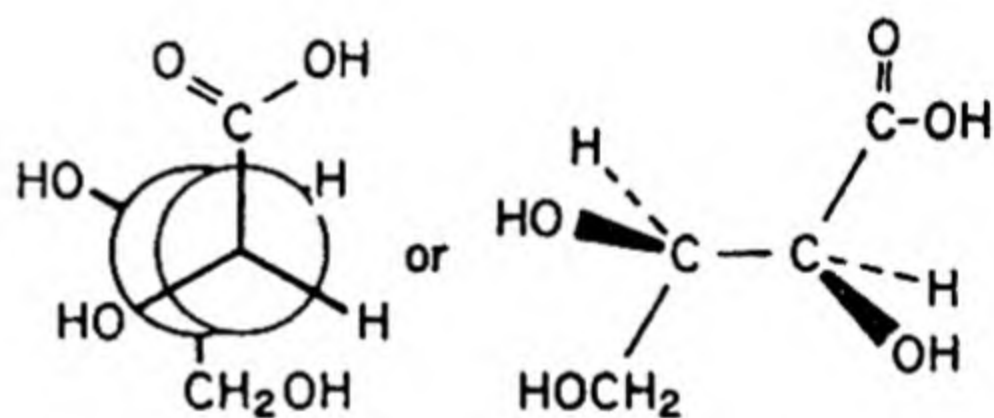
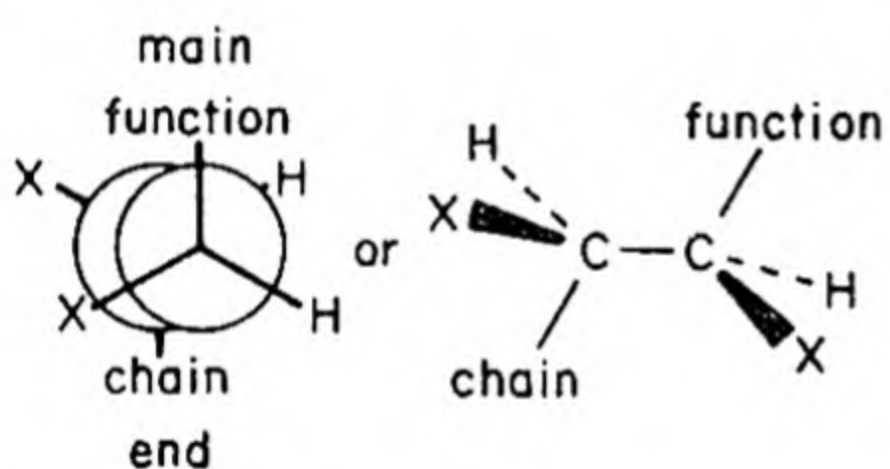
D-erythro:



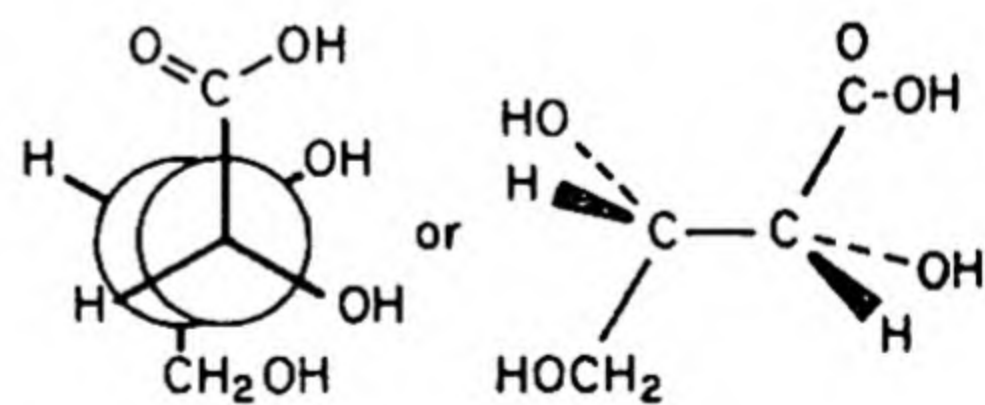
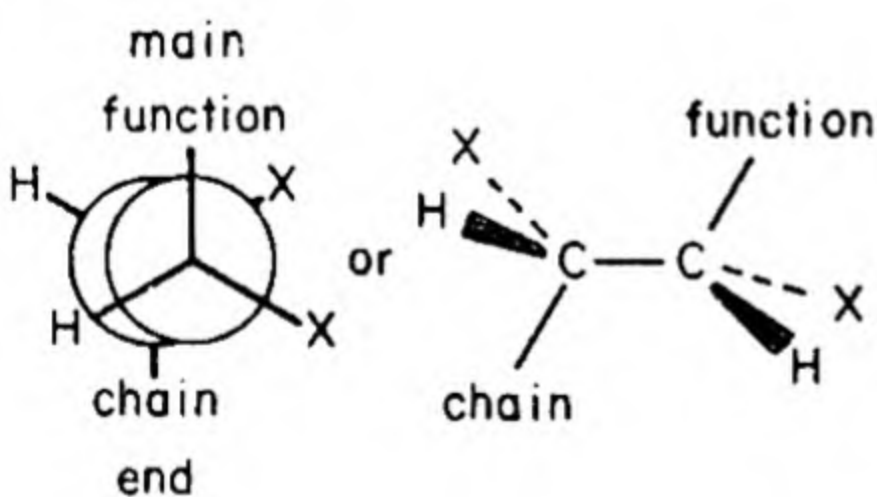
L-erythro:



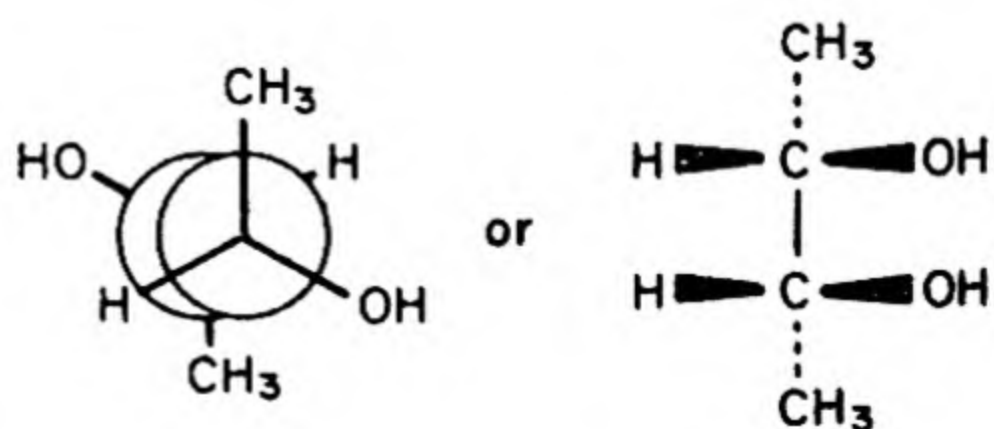
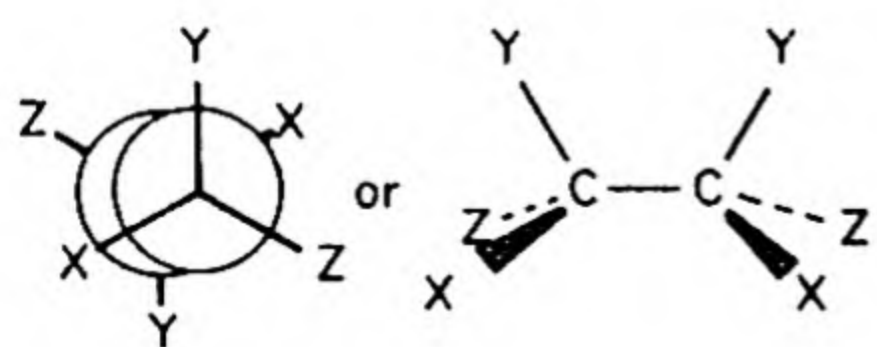
D-threo:



L-threo:

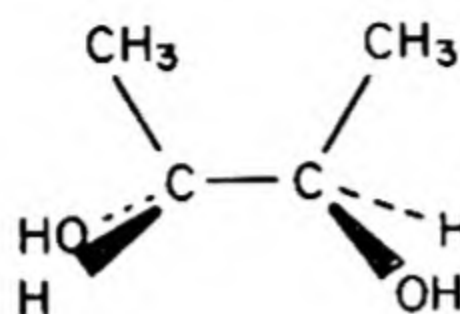
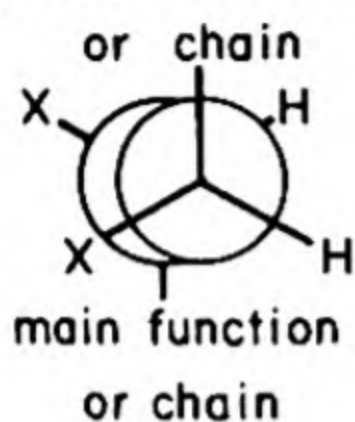


meso:

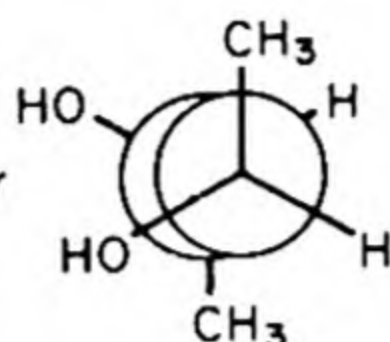


D:

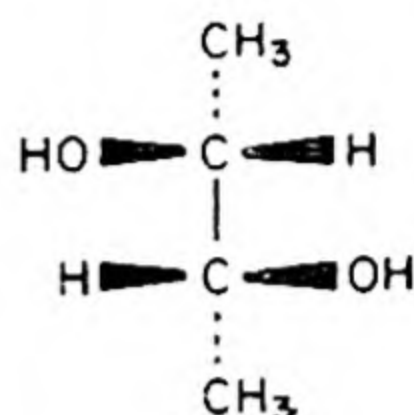
main function



or

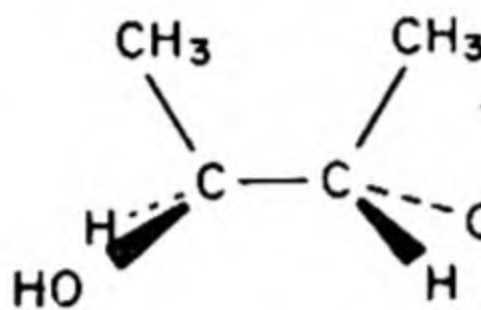
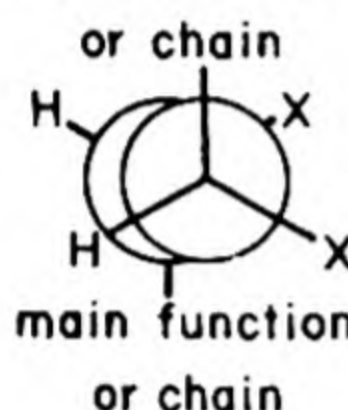


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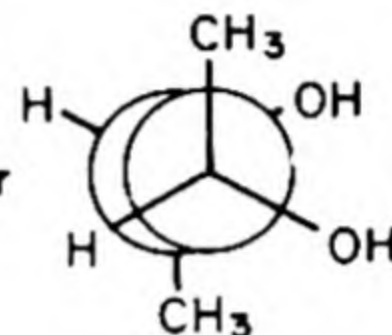


L:

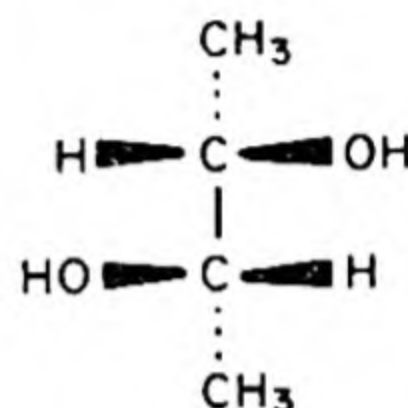
main function



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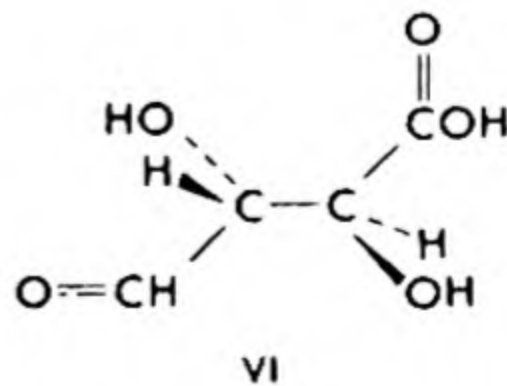
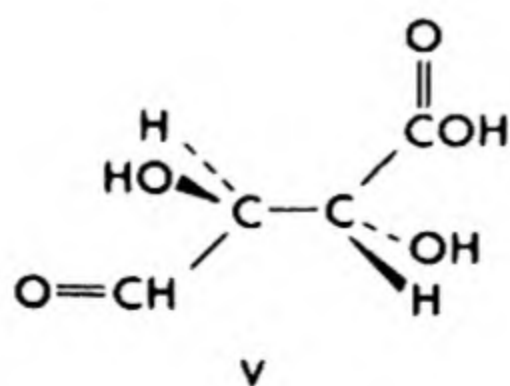
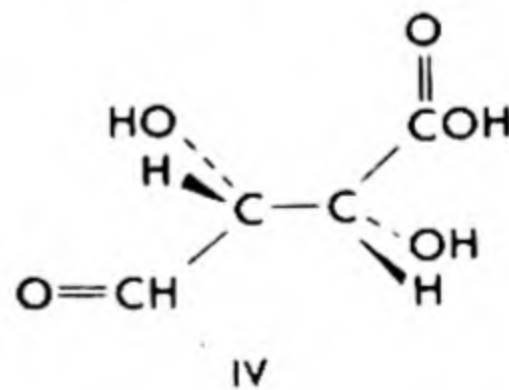
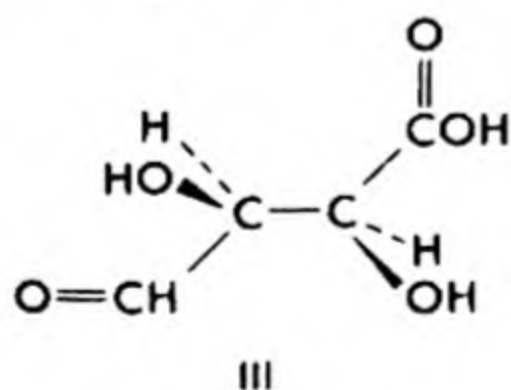
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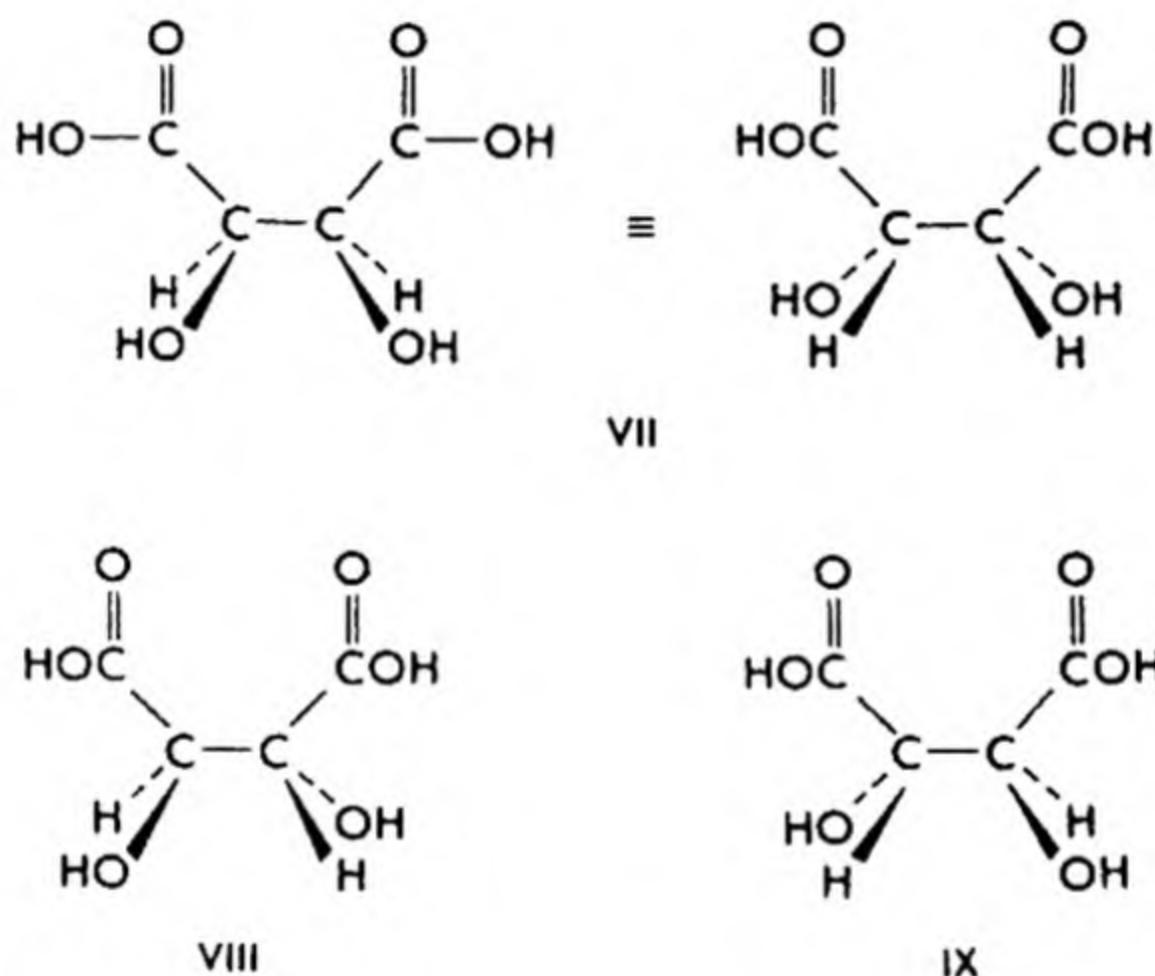
31-5 ASYMMETRIC CARBON ATOMS

Compounds which have only one asymmetric carbon atom must be optically active. Each molecule having one asymmetric carbon atom has a single optical isomer, its enantiomorph.

Molecules with two asymmetric carbon atoms can differ in configuration about each of them. In general, four optical isomers result. Formulas III and IV represent one pair of enantiomorphs, V and VI a second pair. Compounds V and VI are not enantiomorphous to either III or IV, since half of each molecule in one pair has the same configuration as half of each molecule in the other pair, while the other half differs in configuration. Compounds III and IV are *diastereoisomers* (Gk., *dia*, aside or apart, *stereos*, solid space, + isomer) of V and VI.



Molecules in which two asymmetric carbon atoms contain the same groups, such as the tartaric acids, VII–IX, have similar asymmetric atoms. In such compounds, one expected pair of enantiomorphs becomes a single optically inactive (because its mirror image is superimposable upon it) compound, VII. Such a compound is called a *meso compound* (Gk., *mesos*, middle). It is a *diastereoisomer* of each of the enantiomorphs, VIII and IX. Note (you may need to use molecular models) that VIII and IX each has two carbon atoms of the same configuration. Each of these atoms with the attendant groups rotates plane polarized light in the *same* direction (on the average), so that VIII and IX are optically active. However, the *meso* compound, VII, has two like atoms of *opposite configuration*, one of which rotates light to the left and the other an equivalent angle to the right (on the average). The net rotation is therefore zero, so that a *meso* compound is inactive.



31-6 RACEMIC MODIFICATIONS

Synthesis of compounds from optically inactive starting materials never gives optically active products, as the probability of forming one isomer is exactly the same as that of forming its enantiomorph (outline 1). Hence, ordinary synthesis results in an equimolar mixture of enantiomorphs. This mixture is called *racemic*. Each pair of enantiomorphs forms a racemic modification, for example, III and IV, also V and VI, and VIII and IX.

31-7 ASYMMETRIC MOLECULES WITHOUT ASYMMETRIC ATOMS

It is not necessary to the asymmetry of molecules that asymmetric atoms be present. Other factors can produce molecular asymmetry. For example, allenes, $R_1R_2C=C=CR_3R_4$, are asymmetric as long as the

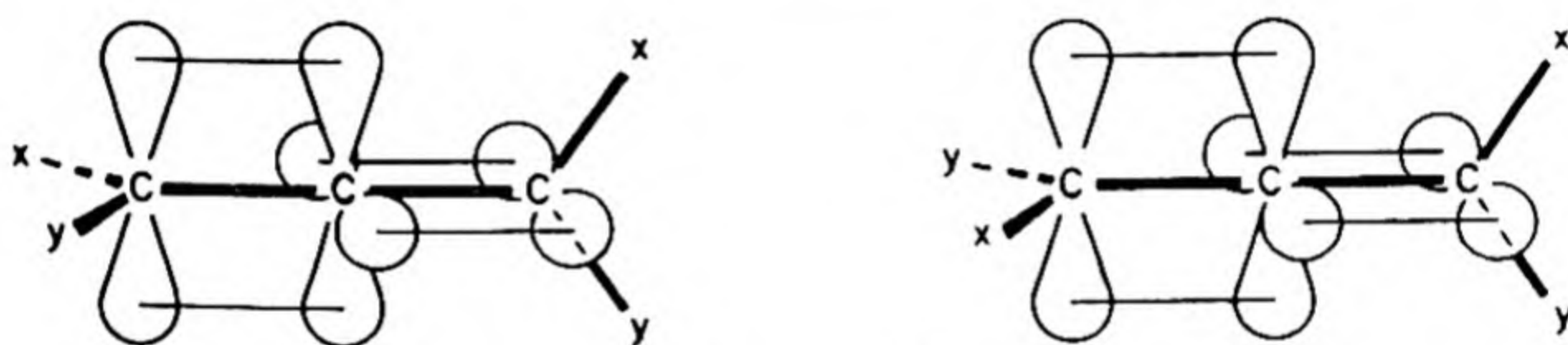
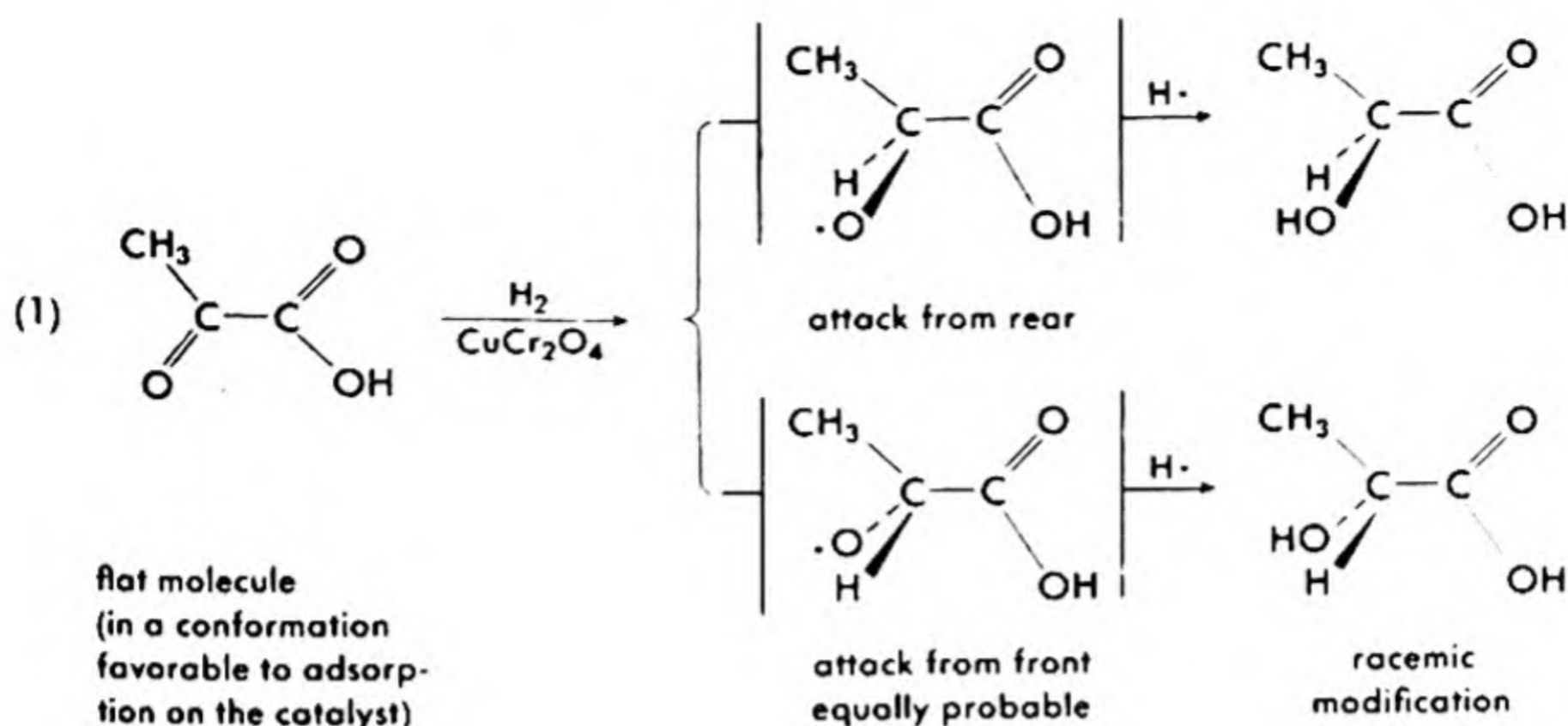
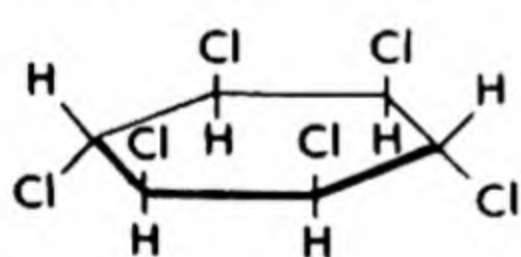


Fig. 31-13. Enantiomorphous Allenes.

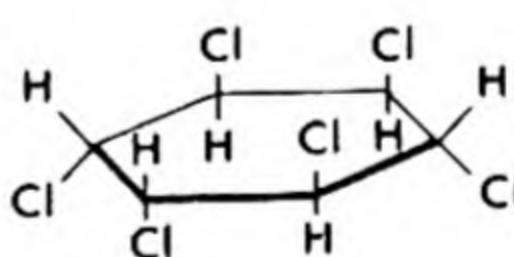
groups, R, on the same end of the cumulated linkage are unlike (Fig. 31-13).

Cis-trans isomerism and optical isomerism are inextricably bound together in such compounds as, for example, the hexachlorocyclohexanes, X, XI, and XII.



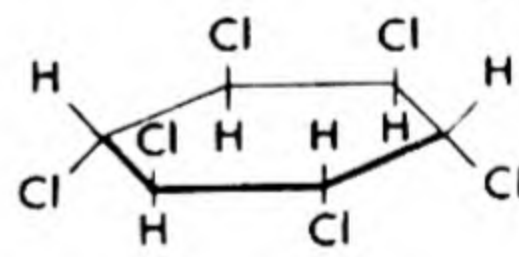
X

γ -(meso) hexachlorocyclohexane (lindane)



XI

racemic hexachlorocyclohexane
(α isomer)



XII

Ortho-substituted biphenyls cannot exist in coplanar conformations if the substituent groups are large enough to prevent rotation around the single bond joining the two rings (Fig. 31-14). Forcing the benzene rings out of coplanarity has readily observable effects on absorption spectra, transfer of reactivity between the rings, and other resonance phenomena.

Optical activity arises when free rotation of the rings about each other is hindered and the molecule is restricted in asymmetric positions. Thus, 2,2'-dichloro-6-bromobiphenyl exists as enantiomorphs XIII and XIV.

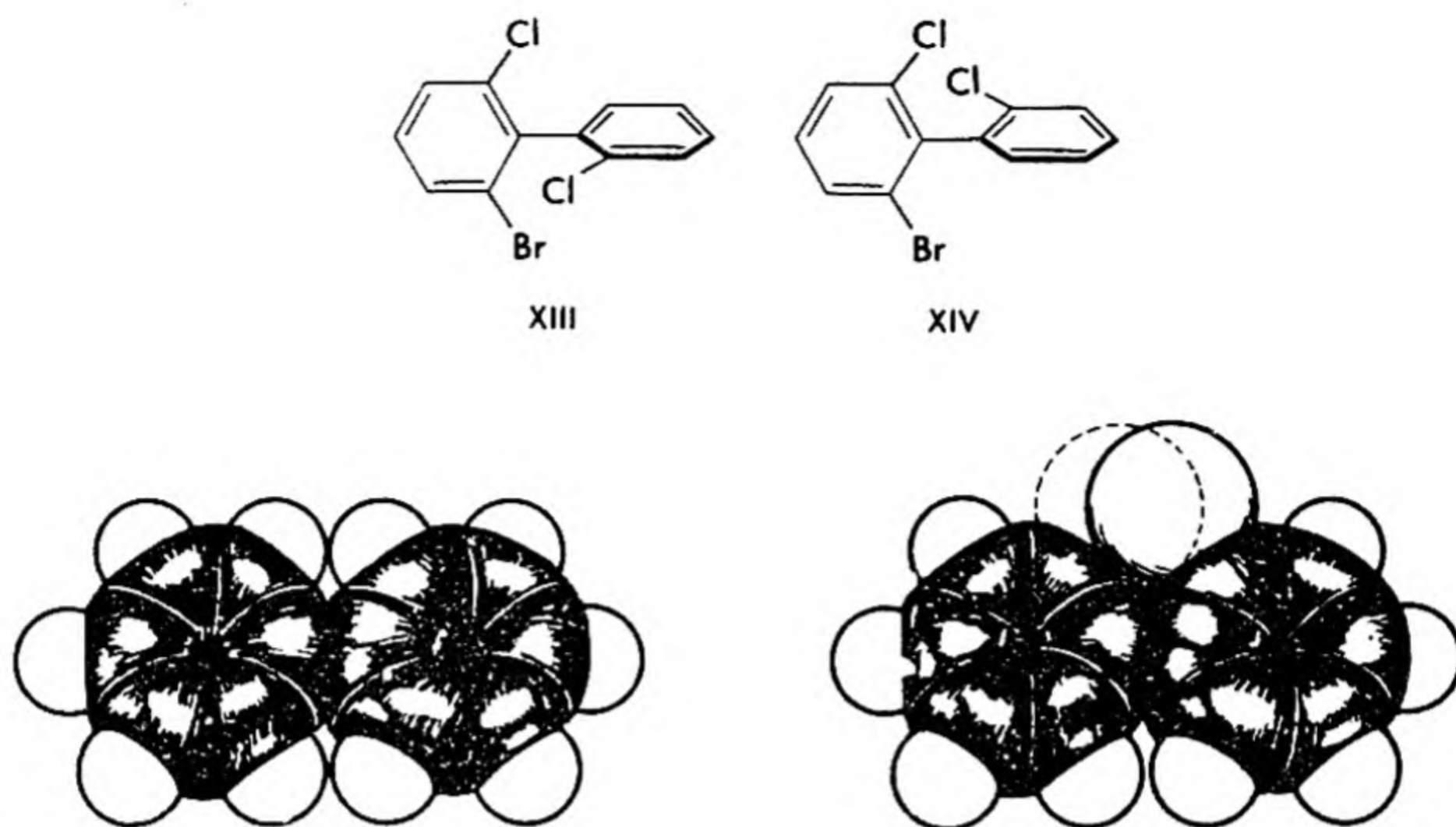


Fig. 31-14. Steric Hindrance in *o,o'*-Dichlorobiphenyl. (A) Unhindered biphenyl, (B) Overlapping of chlorine atoms preventing coplanarity of rings.

31-8 PHYSICAL PROPERTIES OF OPTICAL ISOMERS

Enantiomorphs have exactly the same geometries, since the bond angles and all interatomic distances are identical. The only difference is that the order of angles and distances in one compound is the reverse, or mirror image, of that in its enantiomorph. Thus, physical properties, such as melting point, density, solubility, and refractive index in unpolarized light, which do not depend on asymmetric measurements, are identical for the two, but properties which depend on asymmetric measurements, such as rotation of plane-polarized light, are equal, but opposite, for enantiomorphs.

Diastereoisomers do not have exactly the same geometries. They differ in all physical properties, though the differences are often small. Their optical activities are not equal and may be either the same or opposite in sign.

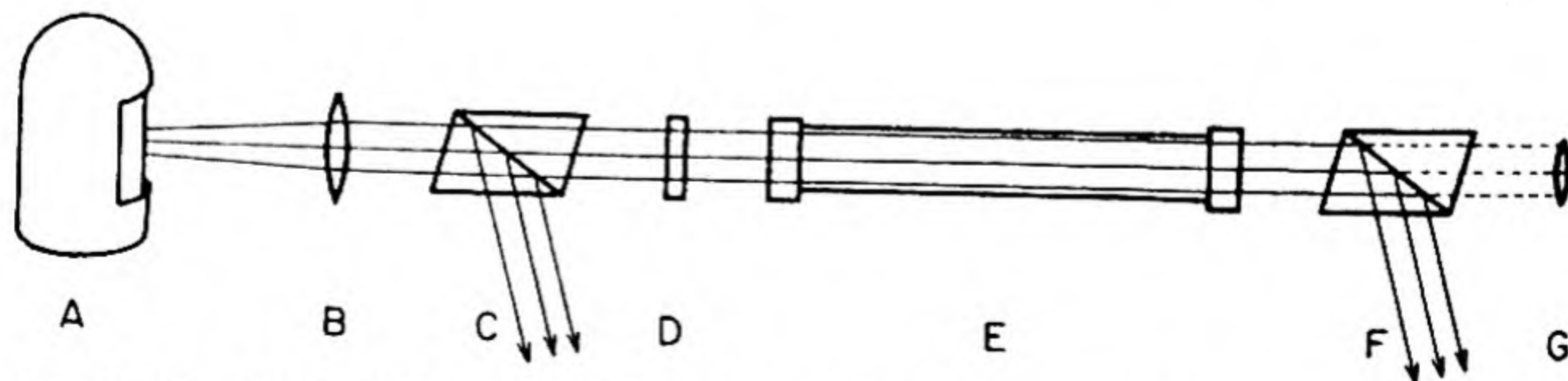


Fig. 31-15. Optical System of Polariscopes. (A) Sodium vapor lamp, (B) Collimating lens, (C) Polarizer, (D) Quartz half-disc endpoint device, (E) Cell containing specimen, (F) Analyzer, (G) Ocular.

Optical activity is measured, as it is detected, by the polarimeter. The optical system of a polarimeter is given in diagram in Fig. 31-15. A polarimeter is shown in Fig. 31-16.

The rotation of light by the sample is read from the protractor in degrees. The angle of rotation depends on the nature of the substance,

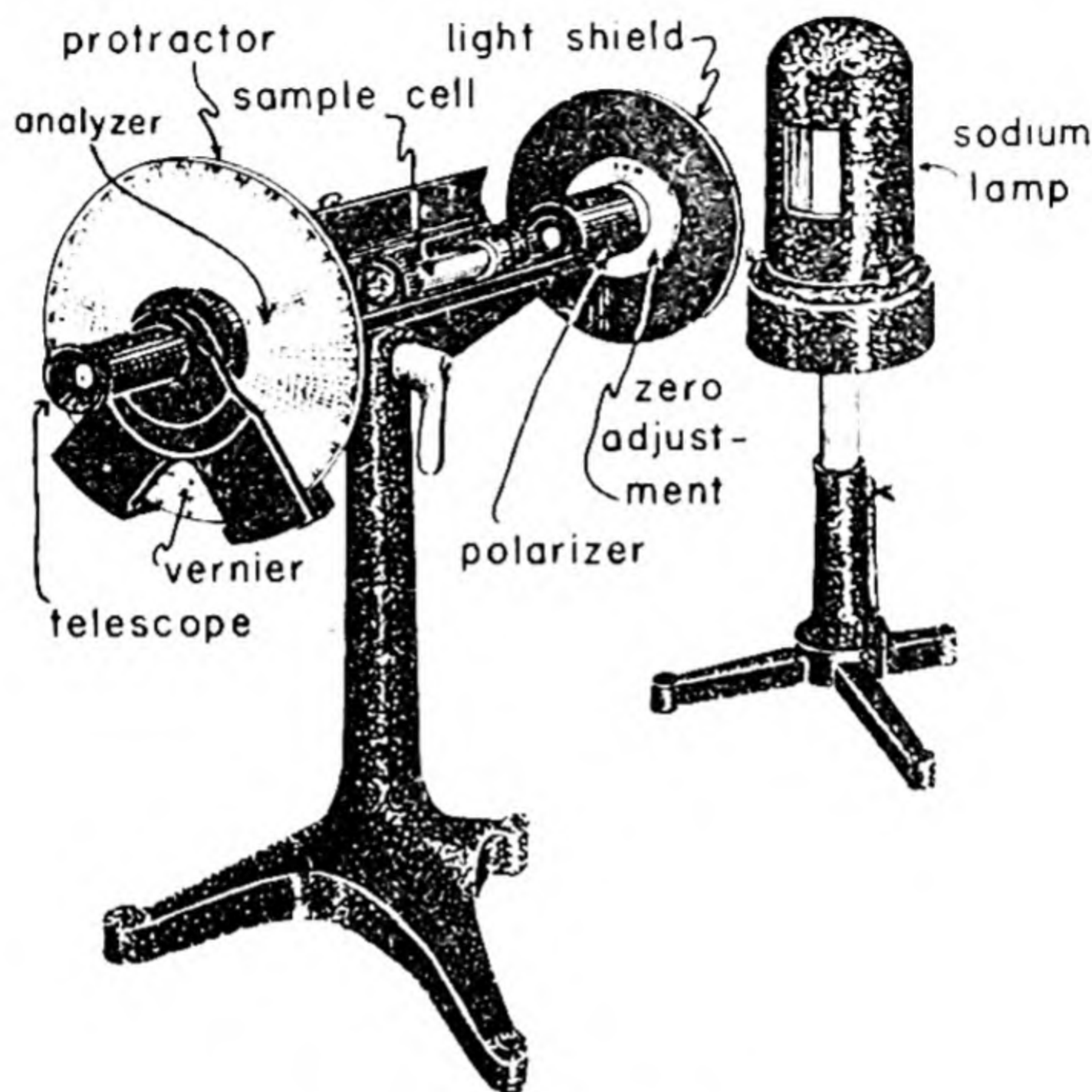


Fig. 31-16. Polarimeter.

the concentration of the specimen, and the length of the path of light through the specimen. To eliminate all of these variables but the nature of the substance, the specific rotation, $[\alpha]$, is defined by eq. (2).

$$(2) \quad [\alpha]_D^t = \frac{\alpha v}{lg}$$

The length of the cell, l , in dm (decimeter), and the concentration in g grams in V ml. of the solution are thus compensated in their effect on the angle of rotation, α . Other factors which influence $[\alpha]$ are temperature, the wavelength of light, and the solvent. These must be specified for any specific rotation. Molecular rotation, $[\phi]$, is the specific rotation times one hundredth of the molecular weight (eq. 3)

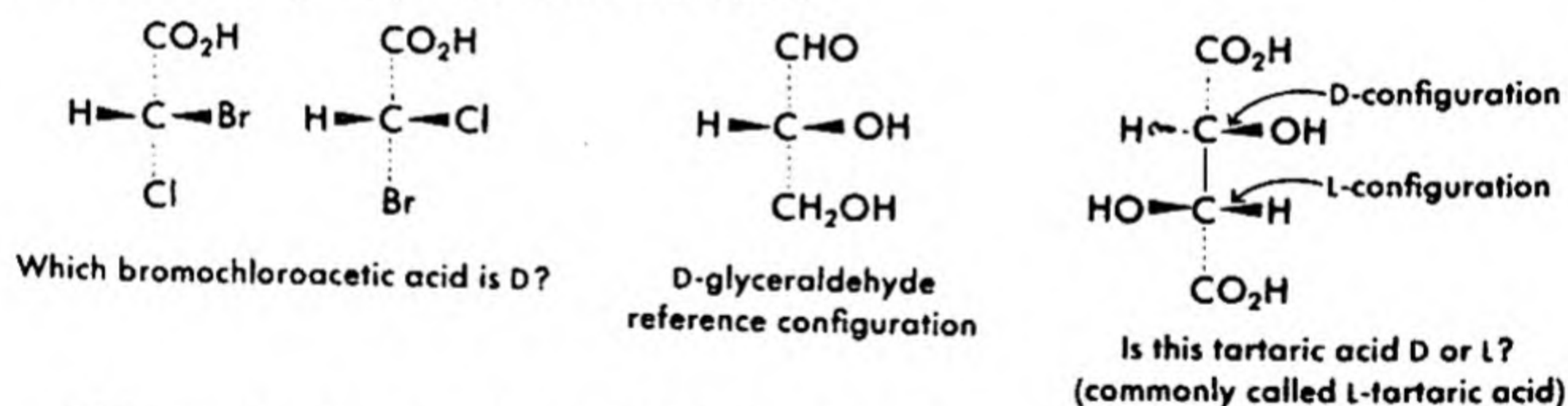
$$(3) \quad [\phi]_D^t = \frac{M\alpha v}{100 lg} = \frac{10\alpha}{lM}$$

in which M is the molar concentration of the solution, M the molecular weight of solute.

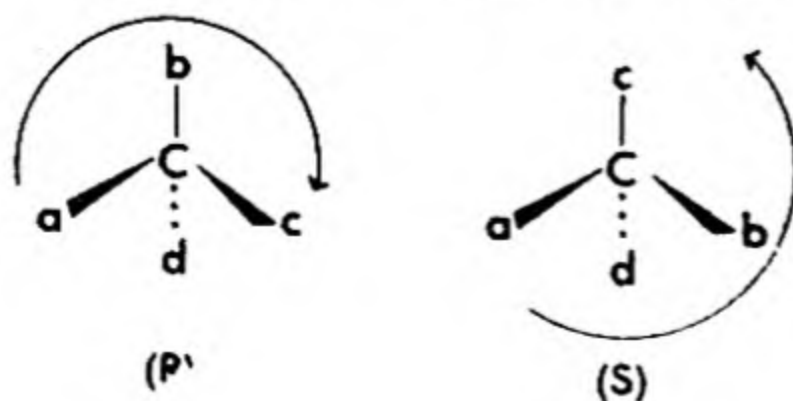
Compounds with clockwise, or positive, specific rotations are termed *dextro*; those with counterclockwise, or negative, specific rotations are termed *levo* (or *laevo*). The direction of rotation is that observed as one looks through the analyzer toward the light source.

At first organic chemists designated optically active isomers with the prefixes *dextro* and *levo*, usually abbreviated d and l . Then D and L became associated with molecular configurations rather than specific rotations. Usually capital letters were used for this, but not always. Since configurations have little relationship to optical rotation, the result was confusion in the chemical literature, with almost complete loss of the significance of d and l . To bring order back to optical rotation nomenclature, letters D and L (capitals) were assigned to indicate configurational relationship only. To designate the direction of specific rotation, positive and negative signs are used. Racemic modifications are indicated by the use of both letters. Thus, $D(+)$ glyceraldehyde is the type substance for the D series, and is dextrorotatory; $L(-)$ glyceraldehyde is its enantiomorph. DL -Glyceraldehyde is the racemic modification.

The practice of designating the configuration of an optical isomer by comparison with a standard reference compound leads to ambiguity in cases where it is difficult to decide which groups are related, as in bromochloroacetic acid, or which of several asymmetric carbon atoms should be the reference group, as in tartaric acid.

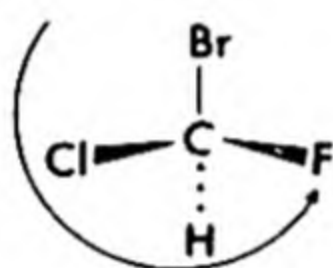


This ambiguity can be avoided by the use of absolute configurations, rather than relative configurations, and the following conventions. The asymmetric center is positioned so that the bond to one attached group, d , points down away from the observer. An arbitrary scale of priorities is assigned to the four groups, a , b , c , and d , and d is the group with the lowest priority. A curved arrow is drawn from the group of highest priority, a , past b to the group of next to lowest priority, c . If the

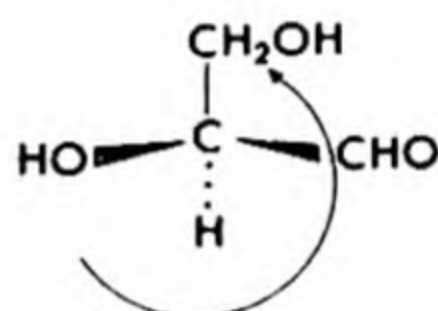


arrow points clockwise the asymmetric atom is termed (R) (L., *rectus*, to the right). If the arrow points counterclockwise, the asymmetric atom is termed (S) (L., *sinister*, to the left). Each asymmetric atom, located by its position number, is designated (R) or (S) in turn in a molecule with several asymmetric atoms.

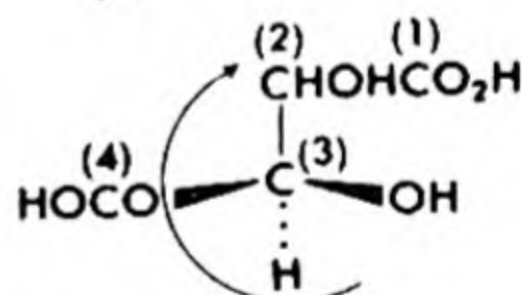
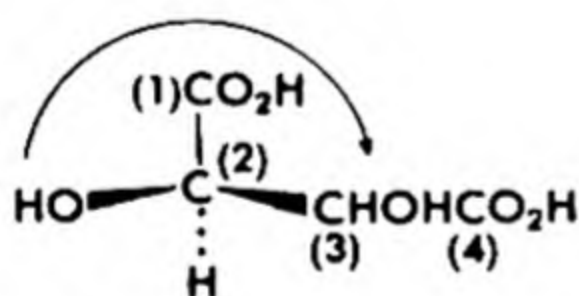
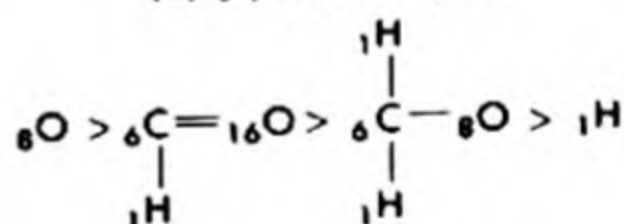
The arbitrary priority assignments are based on atomic numbers of the attached groups. Priority of $a > b$ if the atomic number of $a > b$; thus, $\text{Cl} > \text{OH}$. If a and b have the same atomic number, the atomic numbers of the next atoms attached are considered; $-\text{O}-\text{C} > -\text{O}-\text{H}$. Multiple bonds are considered in their multiplicities; thus $-\text{C}=\text{O}$ has a weight for oxygen of 16 (2×8) and $-\text{C}\equiv\text{N}$ one of 21 for nitrogen, for example. One considers as many of the atoms in a chain as is necessary to find a difference in atomic number. An unshared electron pair is considered to have an atomic number of zero. Thus, the priority of $-\ddot{\text{O}}-\text{H} > -\ddot{\text{O}}:_{(0)}$ as the atomic number of H is greater than that of the electron pair which replaces it on the oxide ion. Some examples which illustrate the method follow.



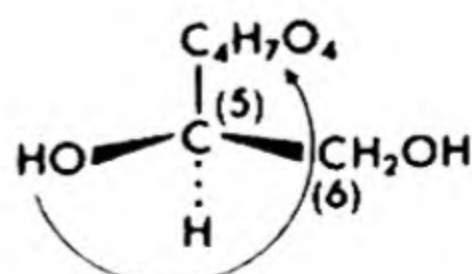
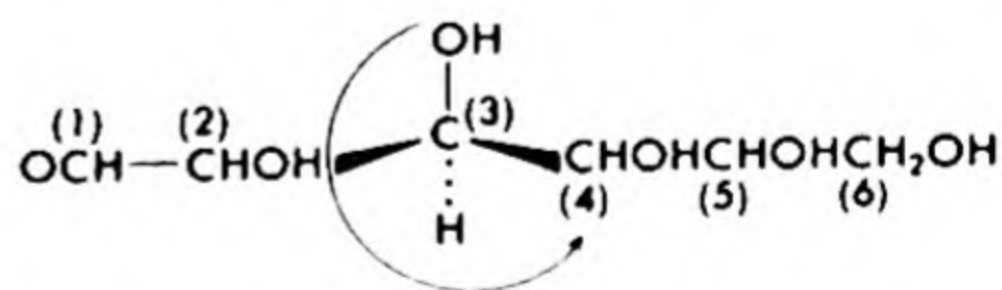
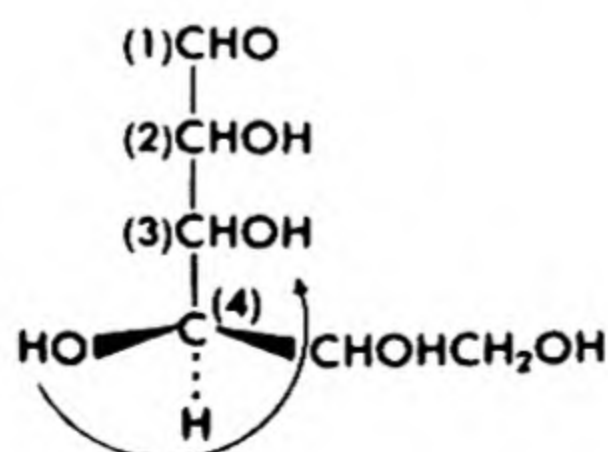
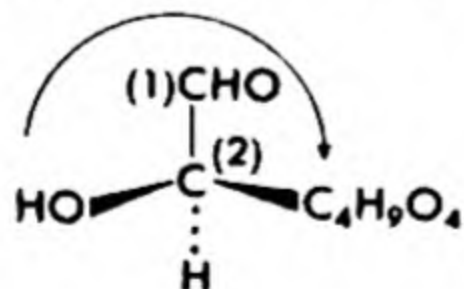
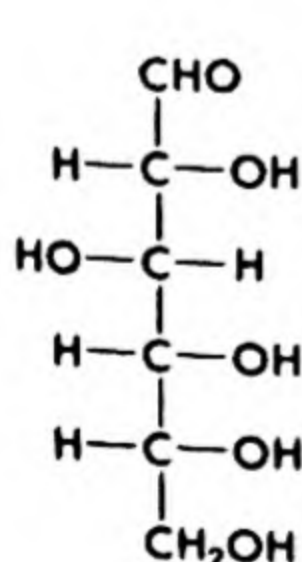
(S)-bromochlorofluoromethane
 $_{35}\text{Br} > _{17}\text{Cl} > _9\text{F} > _1\text{H}$



(S)-glyceraldehyde



2(R), 3(R)-tartaric acid (identical to the D? or L? tartaric acid on p. 624)



glucose

2(R), 3(S), 4(S), 5(S)-2,3,4,5,6-pentahydroxyhexanal

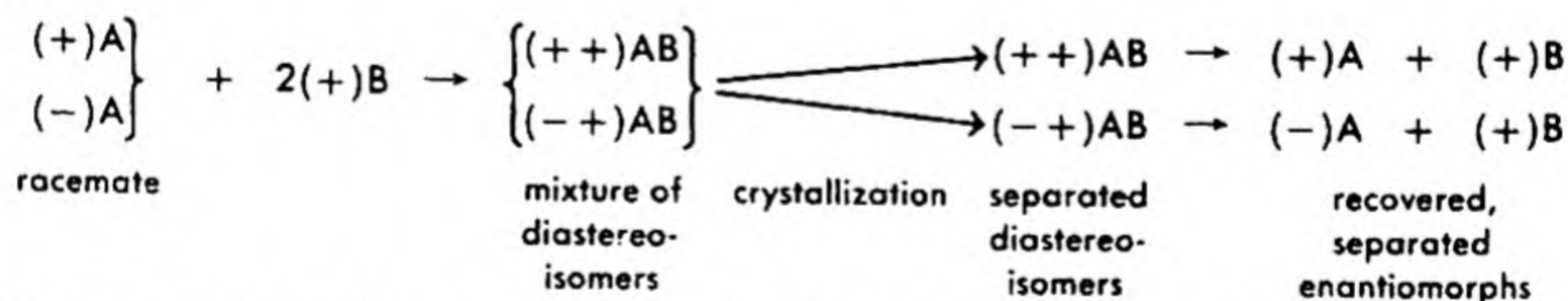
31-9 PREPARATION OF OPTICALLY ACTIVE COMPOUNDS

Since ordinary syntheses give racemic modifications, optically active compounds must be prepared by special methods. The first approach is usually *resolution*, or separation of enantiomorphs. Occasionally, one may use asymmetric synthesis or direct preparation of optically active material by special means.

Resolution can be accomplished in several ways. The most obvious is Pasteur's separation of asymmetric crystals. This mechanical separation is possible only when the racemate is a solid racemic mixture, which is relatively rare. Furthermore, it is practicable only when the crystals are large enough to be handled readily and the differences between enantiomorphous crystals apparent enough to be clearly visible under a magnifying glass.

A second method of resolution is preferential crystallization. A solution supersaturated in both enantiomorphs is carefully seeded with a crystal of one pure enantiomorph and allowed to crystallize. Careful manipulation may prevent the other enantiomorph from crystallizing before the separation can be carried out. If the operator is successful in this, he can recover the second enantiomorph readily by crystallizing it from the solution now depleted in the first. This method also is possible only with enantiomorphs that crystallize as racemic mixtures.

A third, most widely used, method of resolution depends on conversion of the enantiomorphs to diastereoisomers by salt formation, esterification, or other reaction with an optically active pure isomer. Diastereoisomers have different physical properties, such as solubilities or boiling points, hence are more readily separated than enantiomorphs. Eq. (4) represents the scheme of separation of a racemic acid by the use of an optically active



base. Recovery of the desired optically active compounds in the last step demands the use of chemical reactions which are readily reversible. One limitation of this method is that some compounds, such as hydrocarbons, halides, and nitro compounds, do not undergo reactions to form diastereoisomers from which the original compounds can be readily recovered after the separation. Nevertheless, this is the most general of all the methods of resolution.

Another, less commonly used method is kinetic selection. An optically active reagent differs in its rate of reaction with enantiomorphs, since the transition states are diastereoisomers with different geometries, hence

have different steric factors. For example, α -hexachlorocyclohexane, XI-XII, has been resolved by selective dehydrohalogenation of the (+) isomer by brucine, a basic alkaloid. The (–) isomer reacts less rapidly, hence is recovered.

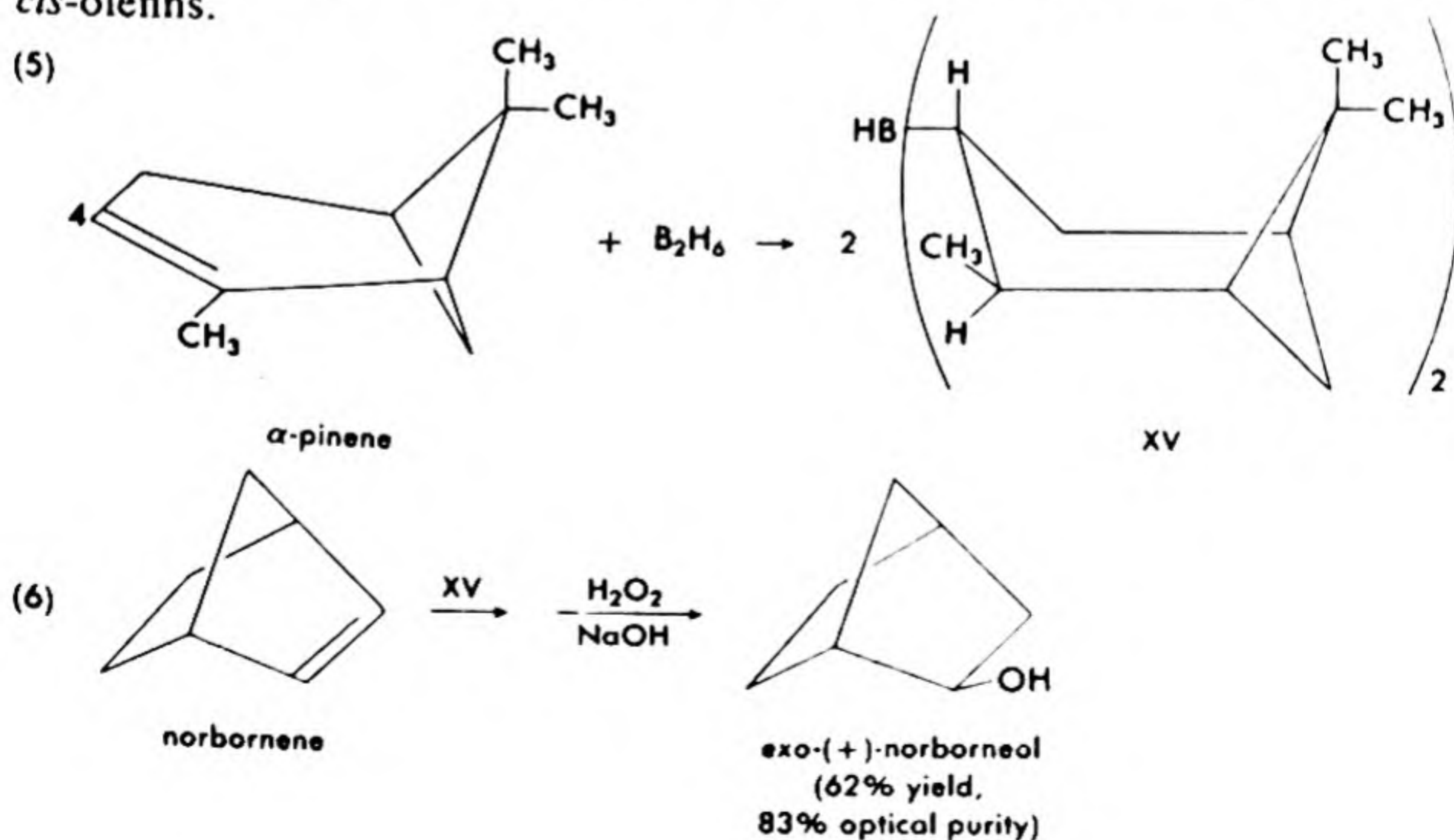
A more common variant of the kinetic method is to feed bacteria or other microorganisms on the racemic modification in the hope that they will feed upon, or metabolize, one form and destroy it, but leave the other behind unchanged. This is a legitimate hope when the compound is a normal food, or a good substitute thereof, since biological processes are very selective between enantiomorphs because of the many asymmetric centers in their optically active enzymes.

Several means of performing asymmetric syntheses are known. Three involve at least transitory formation of diastereoisomers in which properties and positions do not have identical relationships, and thus more of one kind is formed than another.

All biochemical reactions in living organisms use the principle of optically active catalysis. Because of the large number of asymmetric groups present in them, enzymes effect completely asymmetric syntheses. In the laboratory, however, the best the synthetic chemist has been able to accomplish using an optically active catalyst is a slightly greater concentration of one enantiomorph than of the other.

Another method about equally effective in the laboratory as that above is use of an optically active solvent.

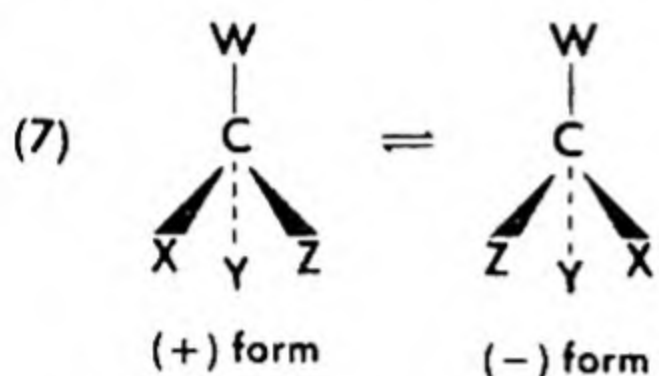
A third method uses optically active reagents, for example, hydroboration by means of an optically active substituted borane rather than diborane. This procedure utilizing diisopinocampheylborane, XV, has afforded optically active alcohols in better than 80% optical purity from *cis*-olefins.



A. Racemization

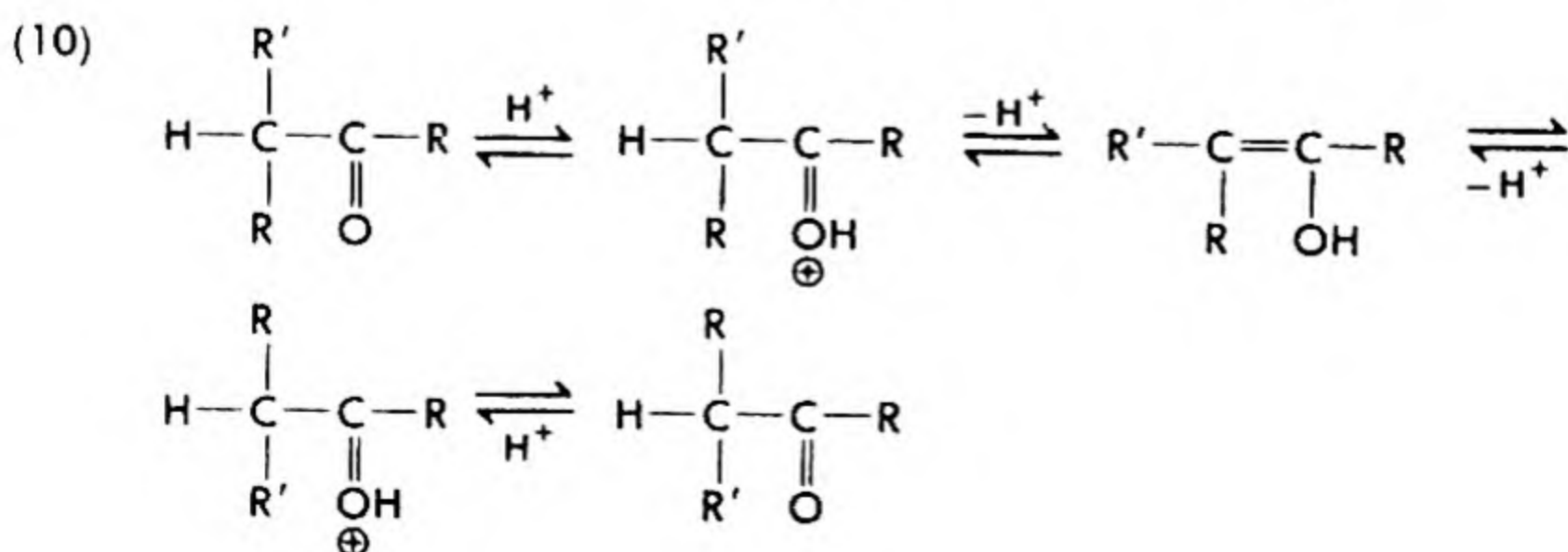
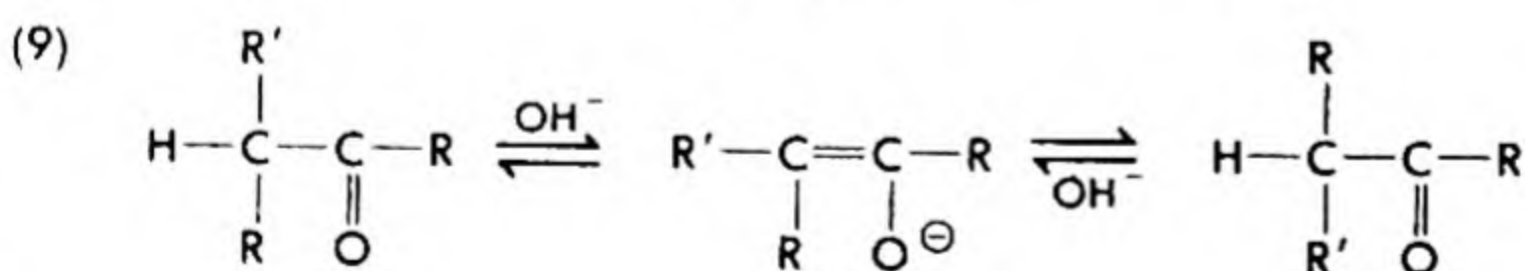
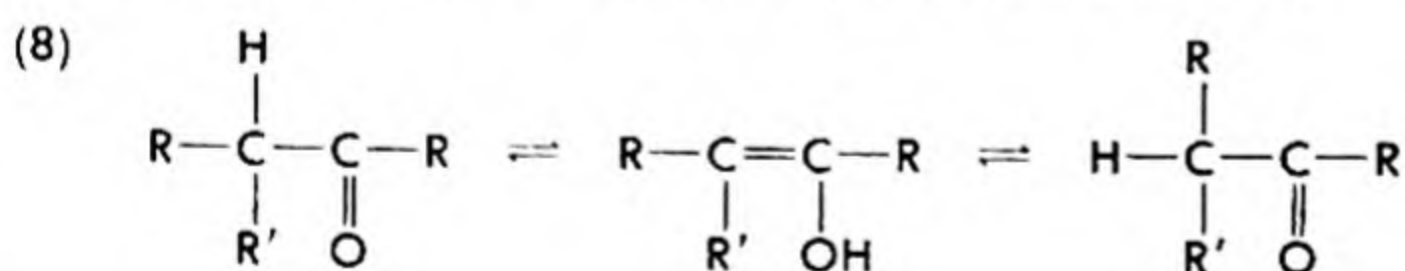
Related to the problem of obtaining enantiomorphs is *racemization*. Stereochemical theory predicts several types of isomers which have proved experimentally to be either incapable of separation or so rapidly interconvertible that they cannot be kept long after isolation. The reason is easy racemization of isomers.

Racemization is the conversion of an optically active material into the racemic modification. In general, the process can be represented as given in eq. (7). One bond to C has been broken and formed again on the opposite side.

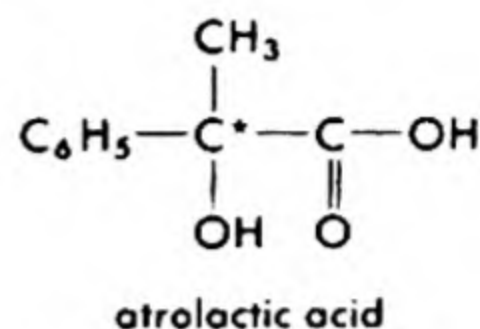
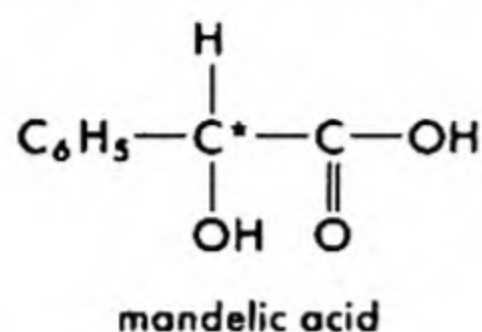


For example, optically active alcohols with the hydroxy group on the C* are racemized in the presence of acidic catalysts. The catalyst promotes carbonium ion formation. Return of the water molecule may occur from either side of the planar carbonium ion (§12-1B(2)).

Among short-lived optically active compounds are those which have as asymmetric centers carbon atoms adjacent to carbonyl groups. Enolate ions and enols are inactive, hence racemization occurs readily (eq. 8). Since acids and bases tend to induce enolization (§21-2), they hasten racemization of α -C* compounds (eqs. 9 and 10).



When no hydrogen atom is present on the C^* , tautomerism cannot occur, and the optically active compound is stable. Thus, mandelic acid racemizes quickly, but atrolactic acid does not.



B. Racemization in Nitrogen Compounds

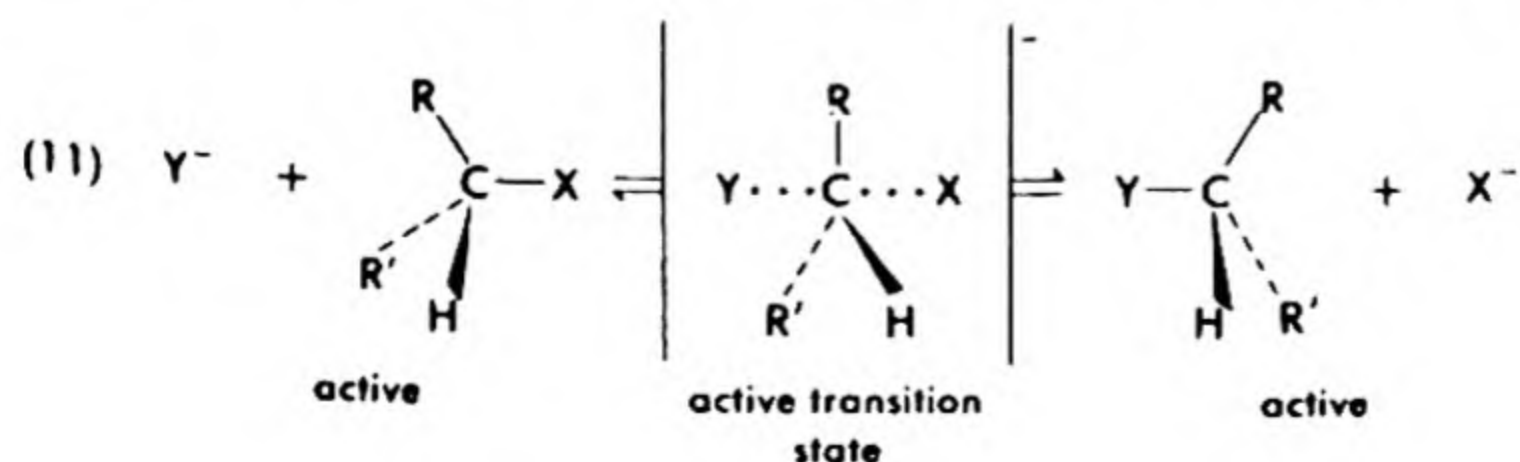
Since nitrogen compounds are shown by their polar nature to contain pyramidal molecules with nitrogen atoms at the apices, it was anticipated that tertiary amines with three different alkyl groups ought to be resolvable into active forms. The situation is analogous to asymmetry of carbon atoms, if the unshared pair of electrons on the nitrogen atom is considered as a fourth group. However, it is relatively easy for simple amines to invert their configurations; in fact, ammonia and its derivatives oscillate back and forth with complete reversal of configuration at each oscillation. In ammonia itself, the inversion occurs 1900 times a second (950 cycles a second) at 0° .

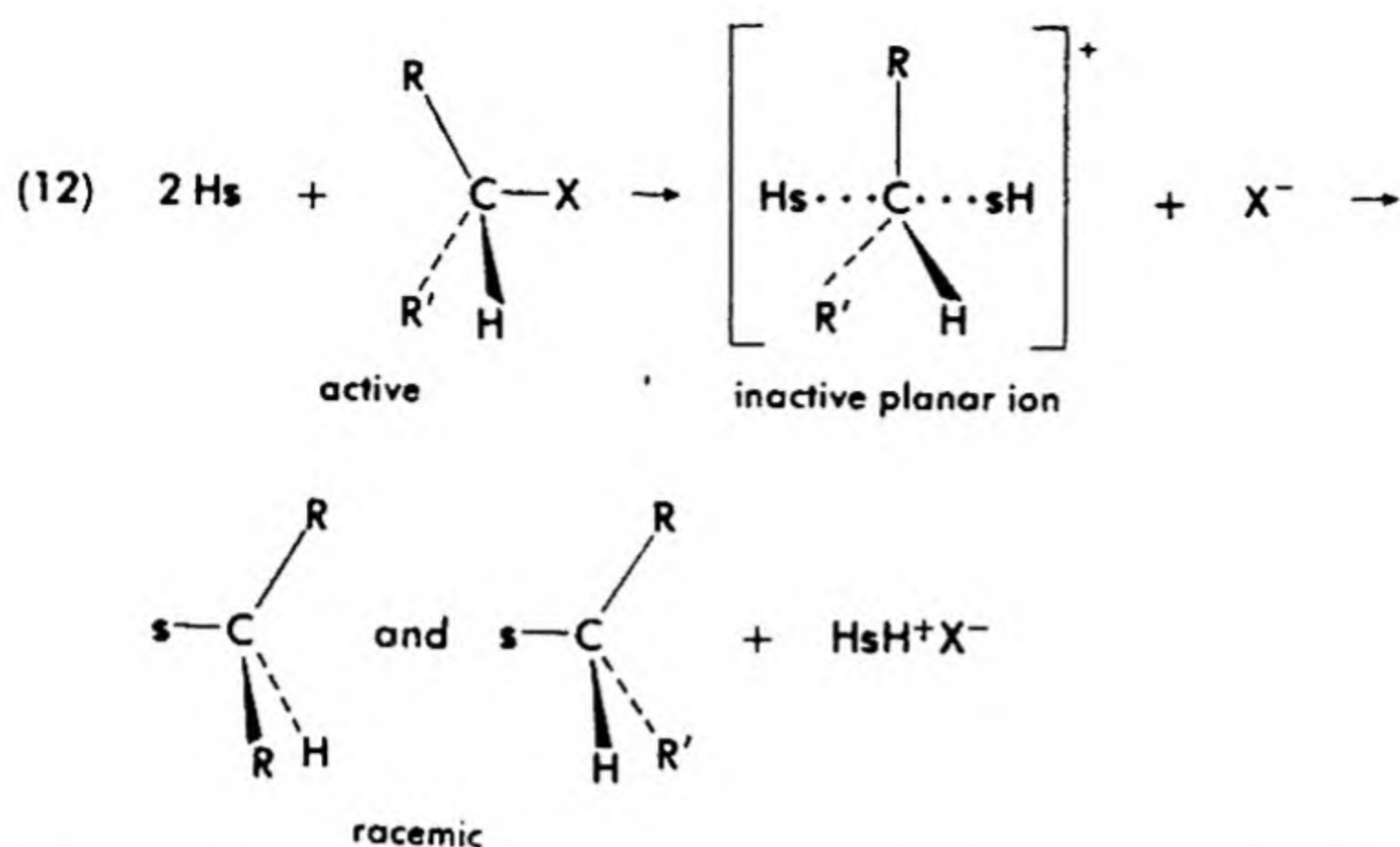
In quaternary ammonium ions, the presence of four groups localizes valence forces so that inversion or racemization is as difficult as with related carbon compounds. Consequently, compounds containing such ions have been readily resolved.

C. Walden Inversion

It is not always necessary to prepare optically active compounds from inactive raw materials. It is quite practicable to convert one optically active compound to another by ordinary chemical reactions. When the functional group attacked is remote from asymmetric carbon atoms, racemization is seldom a problem. However, if a group on the C^* is replaced, racemization will occur if an optically inactive intermediate is formed.

As has been mentioned (§12-1B(2)), one method of determining the mechanism by which a reaction occurs is to study the effects of the re-

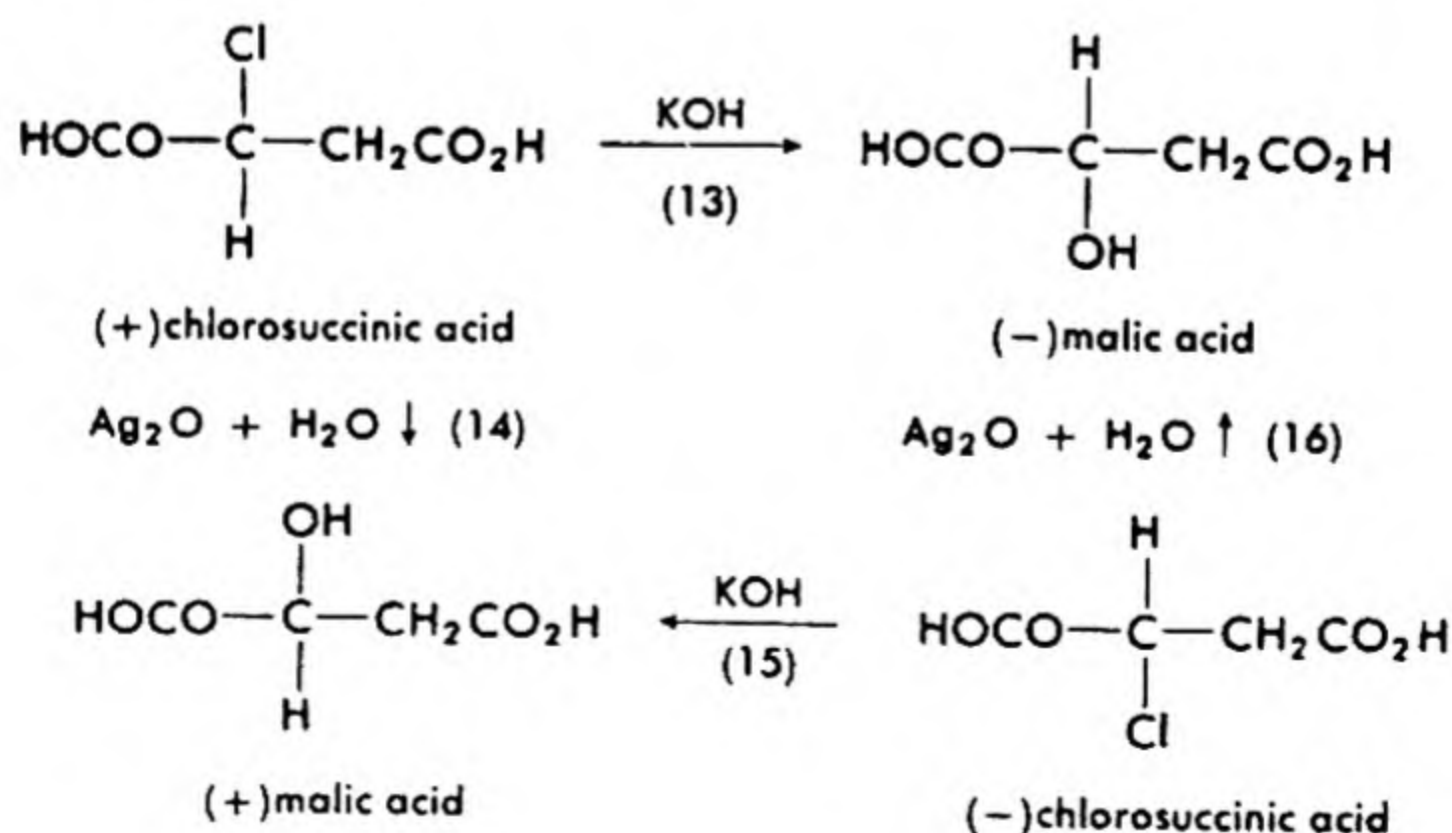




action on optically active compounds. The direct displacement mechanism (eq. 11) gives optically pure product, whereas the carbonium ion mechanism (eq. 12) involves racemization. (Y^- = any nucleophile; Hs = a nucleophilic solvent.)

Although full optical activity is retained in the course of the direct displacement mechanism, the three groups not replaced have been turned inside out like an umbrella in a high wind. The configuration of the product is opposite to that of the starting material. This reversal of configuration during reaction is called *Walden inversion*.

The first evidence for inversion was the observation by Paul Walden (1893) that synthesis of derivatives of optically active compounds by two different routes sometimes produces different enantiomorphs. For example, displacement of halogen in (+)chlorosuccinic acid using potassium hydroxide gives (−)malic acid, (13), but using silver oxide, gives (+)malic acid, (14). The enantiomorphic relationship is also true, (15) and (16). For simplicity, the acids, rather than their salts, are given in these equations.



The explanation is that some reactions involve an even number of Walden inversions (eq. 11), hence result in the same configuration as the original reactant, whereas other reactions involve an odd number of inversions to give the opposite configuration.

SUPPLEMENTARY READINGS

- Cram, D. J., "Recent Advances in Stereochemistry," *J. Chem. Educ.* **37**, 317-321 (1960).
 Eliel, E. L., *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962, Chapters 1-6.
 Shriner, R. L., R. Adams, and C. S. Marvel, "Stereoisomerism," in H. Gilman, Ed., *Organic Chemistry an Advanced Treatise*, 2nd ed., Vol. I, Wiley, New York, 1937, pp. 214-243.
 Wheland, G. W., *Advanced Organic Chemistry*, 2nd ed., Wiley, New York, 1949, pp. 150-333, 351-355.

QUESTIONS AND PROBLEMS

1. Show by explanation, illustration, or definition that you understand what is meant by each of the following terms. Use diagrams wherever it is appropriate, but accompany them with verbal explanation.

- | | |
|---------------------------|--------------------------|
| a. asymmetric molecule | h. plane-polarized light |
| b. asymmetric carbon atom | i. racemic modification |
| c. asymmetric synthesis | j. racemization |
| d. dextrorotatory | k. resolution |
| e. diastereoisomers | l. specific rotation |
| f. enantiomorphs | m. Walden inversion |
| g. meso form | |

2. Without referring to the diagrams in this chapter, sketch the essential parts of a polarimeter and explain how it operates.

3. A solution containing 53.22 mg./ml. of a certain sugar had a rotation of $+9^{\circ} 32'$ in a 20 cm. tube. Calculate the specific rotation of the sugar.

4. A 1% solution in dioxane of estrone benzoate (a hormone) has a rotation of $+2^{\circ} 24'$ in a 20 cm. tube. Calculate the specific rotation of this hormone.

5. Write configurational formulas for all possible optical isomers of the following compounds. Label the racemic pairs, diastereoisomers, meso forms, and enantiomorphs. If the compound has no optical isomers, label it inactive. Place asterisks beside asymmetric carbon atoms.

- | | |
|---|---|
| a. 2-chlorobutane | g. 2,3,4,5-tetrahydroxypentanal |
| b. α, β, γ -trihydroxyglutaric acid | h. 2-bicyclo[2.2.1]heptene |
| c. methyl isopropyl ketone | i. 1,4-bis(2-bromophenyl)-2,3-dinitrobenzene-5,6-dicarboxylic anhydride |
| d. 2,3,4,5-tetrahydroxyhexanedioic acid | j. 2,6,2'-trichlorobiphenyl |
| e. benzene hexachloride | |
| f. 2,4-dichloropentanal | |

6. Write out all possible configurations of 2,4-dibromopentane-3-carboxylic acid. Label asymmetric carbon atoms, enantiomorphs, diastereoisomers, meso forms. If the central (no. 3) carbon atom had no asymmetry at all, as in 2,4-dibromopentane, how many different forms would there be for this compound? How many optical isomers of 2,4-dibromopentane-3-carboxylic acid actually do exist?

7. Write a projection formula to illustrate each of the following concepts.

- | | |
|--|---|
| a. nonasymmetric molecule | c. asymmetric molecule without asymmetric atom |
| b. sterically hindered asymmetric biphenyl | d. optically inactive compound with asymmetric carbon atoms |



Optical Rotatory Dispersion

32-1 DISPERSION

It is a common observation that the index of refraction of a substance depends on the wavelength of transmitted light. The higher refractive indices of shorter wavelengths make possible dispersion of light into a spectrum upon passage through a prism. Similarly, the specific rotation of a substance depends on wavelength, with shorter wavelengths giving higher specific rotations, so long as no absorption of light occurs in the region of study. The change of specific rotation with wavelength is called *optical rotatory dispersion*.

32-2 ABSORPTION OF LIGHT

You are familiar with the fact that the wavelengths of lines in atomic emission spectra are related to energy transitions of electrons from higher to lower energy states. Conversely, if light of the proper wavelength is passed through matter, atoms can absorb the light, using the absorbed energy to acquire an excited state. Thus, electromagnetic energy provided continuously over a range of wavelengths is absorbed by excitable atoms at only those wavelengths corresponding to electronic transitions, resulting in an absorption spectrum. Similar, though more complex, absorption spectra are more often observed in molecules (see Chapter 33).

32-3 THE COTTON EFFECT

Near and through regions of absorption where energy transitions occur, optical rotatory dispersions often behave quite irregularly. They often characteristically pass through one or more maxima ("peaks") and minima ("troughs"). Such irregularities are called the *Cotton effect* (Aimé Cotton, chemical physicist). (See Fig. 32-1.)

If the curve shows a single maximum and single minimum (Fig. 32-1), the curve is a single Cotton effect. Curves with two or more peaks and corresponding troughs for an absorption band are multiple Cotton effects. The Cotton effect is positive when the end toward longer wavelengths is

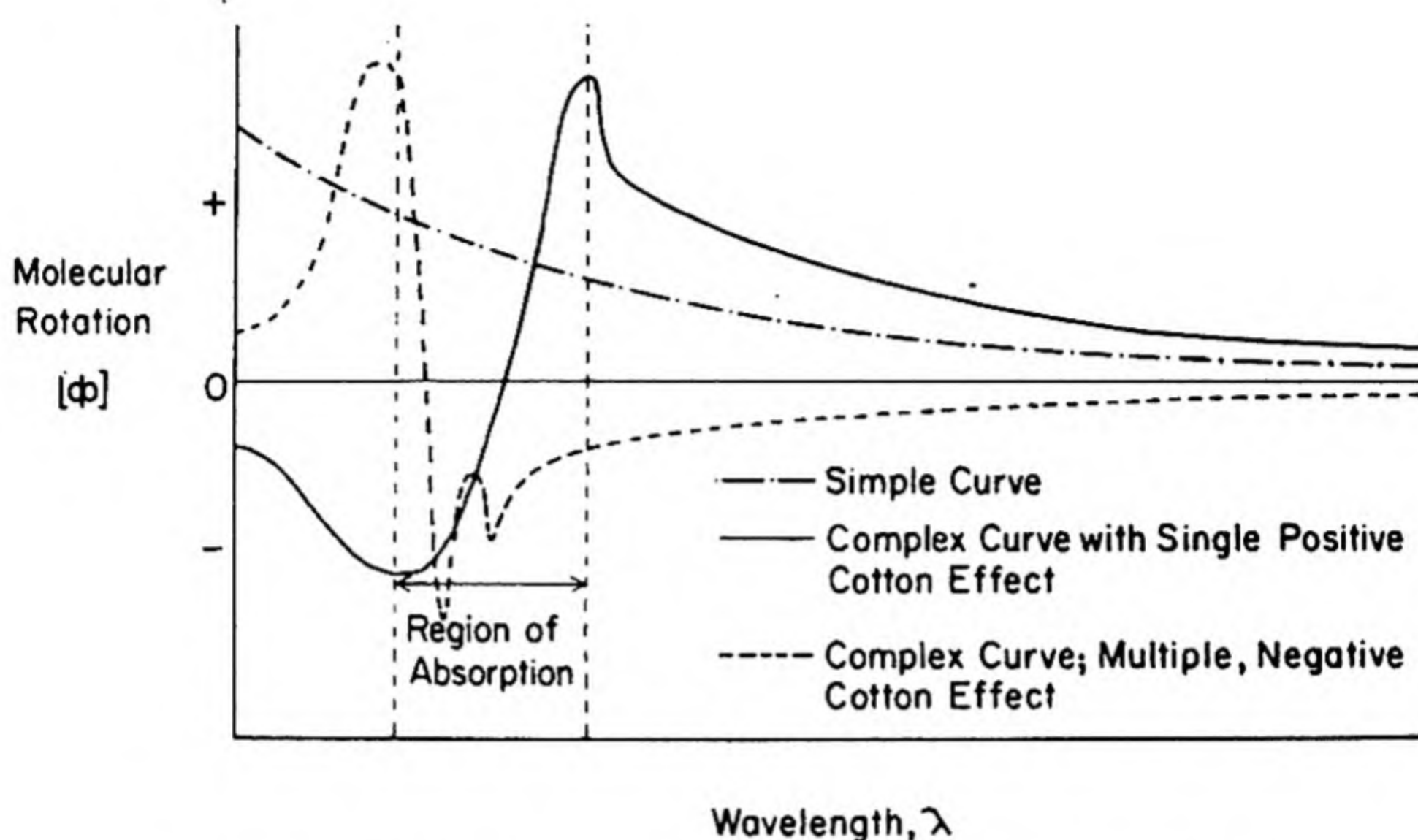


Fig. 32-1. Optical Rotatory Dispersion Showing Cotton Effects.

positive (solid line in Fig. 32-1) and negative when the curve is like the dotted line in Fig. 32-1. One enantiomorph will give a positive Cotton effect, and the other, having equal rotations always of opposite sign, a negative Cotton effect. These effects are related to the orientation of groups in the molecule near the light-absorbing group (chromophore, §33-2E).

32-4 MEASUREMENT OF OPTICAL ROTATORY DISPERSION

Instrumentation for optical rotatory dispersion is a combination of the polarimeter to measure optical rotation, a spectroscope to provide monochromatic light (visible or ultraviolet) of known wavelength, and a photoelectric device to determine the angle of minimum transmittance. The whole instrument is called a *photoelectric spectropolarimeter*.

32-5 STRUCTURE AND OPTICAL ROTATORY DISPERSION

Optical rotatory dispersion has been a powerful tool for the determination of *absolute configurations* of molecules since the first absolute configuration was determined in 1951. Absolute configuration is the actual spatial orientation of groups at an asymmetric center, while relative configuration compares the configuration of a molecule to that of a standard substance, as in the classic sugar studies by Emil Fischer (§38-1B(7)). Thus far, the most successful applications of the optical rotatory dispersion procedure have been to the stereochemistry of cyclohexanones

and complex ring compounds containing the cyclohexanone ring. For this, the octant rule applies.

A. The Octant Rule

When the molecule containing the cyclohexanone ring is oriented as in Fig. 32-2, with the carbonyl group on the origin of the axes, and the molecule divided as shown by Cartesian coordinates into octants, then projected on the frontal plane, P_1 , perpendicular to the $C=O$ bond, the octant diagram (Fig. 32-3) results.

The octant rule for cases in which all ring substituents lie within the rear octants has the following postulates:

(1) Atoms lying in any of the dividing planes make no contribution to the specific rotation. These include the directly connected atoms in 2Re, 2Le, 4a, and 4e positions. The designation 2Re, for example, means the equatorial group on carbon 2 to the right; 3La means the axial group on carbon 3 to the left.

(2) Atoms lying in the upper right octant (above plane P_2 and to the right of P_3), and those lying in the lower left octant (below plane P_2 and to the left of P_3) make negative contributions to the specific rotation. These include groups 3Ra, 3Re, and 2La, as well as any atoms attached to 2Le, 2Re, 4a, and 4e that lie in these octants.

(3) Atoms lying in the upper left octant (above plane P_2 and to the left of P_3), and those lying in the lower right octant (below plane P_2 and to the right of P_3) make positive contributions to the specific rotation. These include groups 3La, 3Le, and 2Ra, as well as any atoms attached to 2Le, 2Re, 4a, and 4e that lie in these octants.

When any ring substituents lie within the front octants (to the left of plane P_1 , Fig. 32-2), the contributions of these groups to the specific rotation are opposite in sign to those of the groups in the octants behind them.

These signs apply to the long-wavelength sides of Cotton effect anomalies; hence, if the sum of contributions is positive, the Cotton effect is positive, and the Cotton effect is negative if the sum of contributions is negative. The applicable Cotton effect is that for an absorption band due to the keto group.

B. Further Conventions

Since spatially opposed like atoms and groups on opposite sides of a reference plane each cancel the contribution of the other, only groups which have no correspondence need to be considered in evaluating the total specific rotation. These are called *significant groups* (or significant atoms). Abbreviated diagrams are derived from the octant diagram in which each significant atom or group is indicated by its arabic position number, if carbon, or arabic position number and symbol, if not carbon.

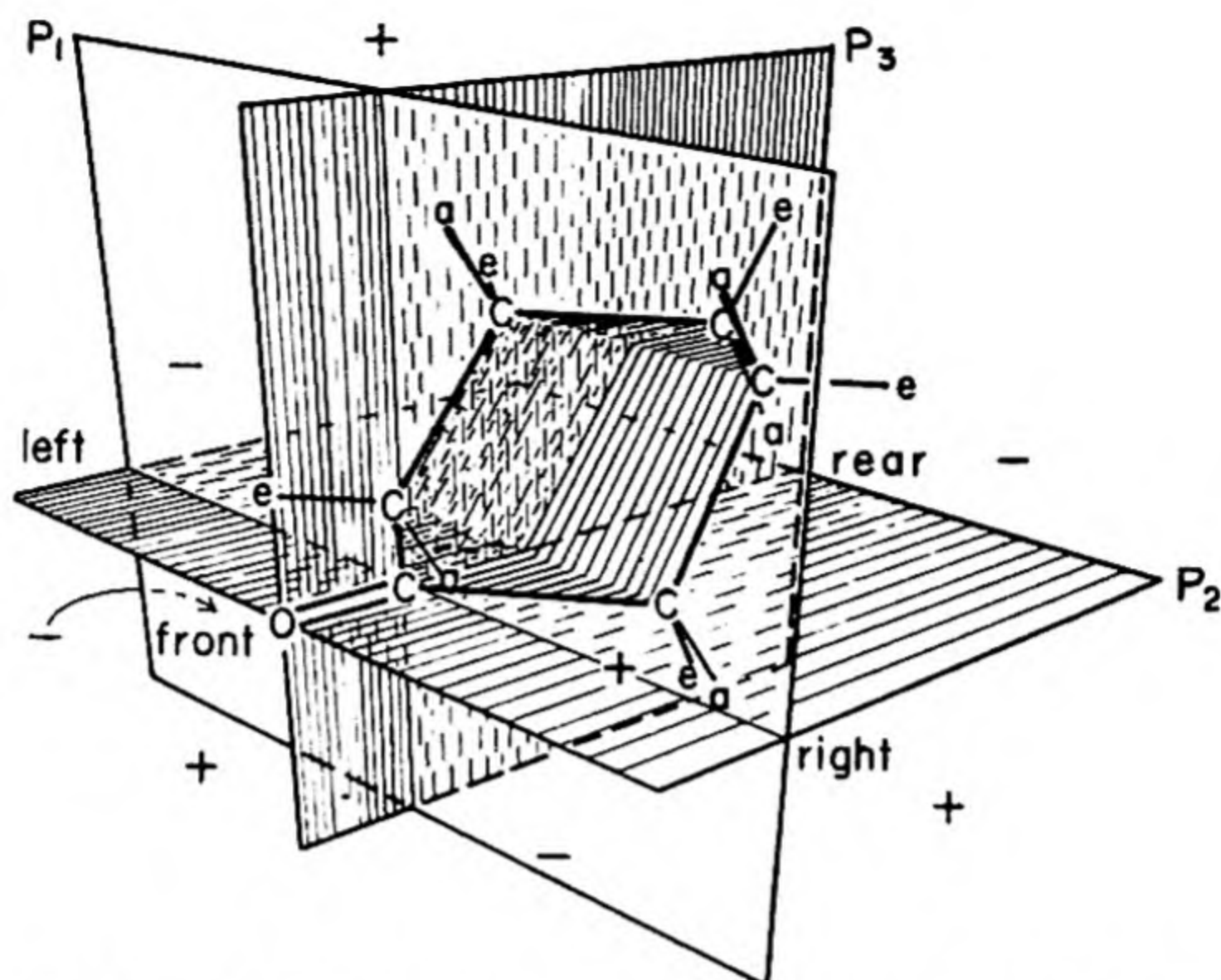


Fig. 32-2. Orientation of a Cyclohexane Ring for the Octant Rule.

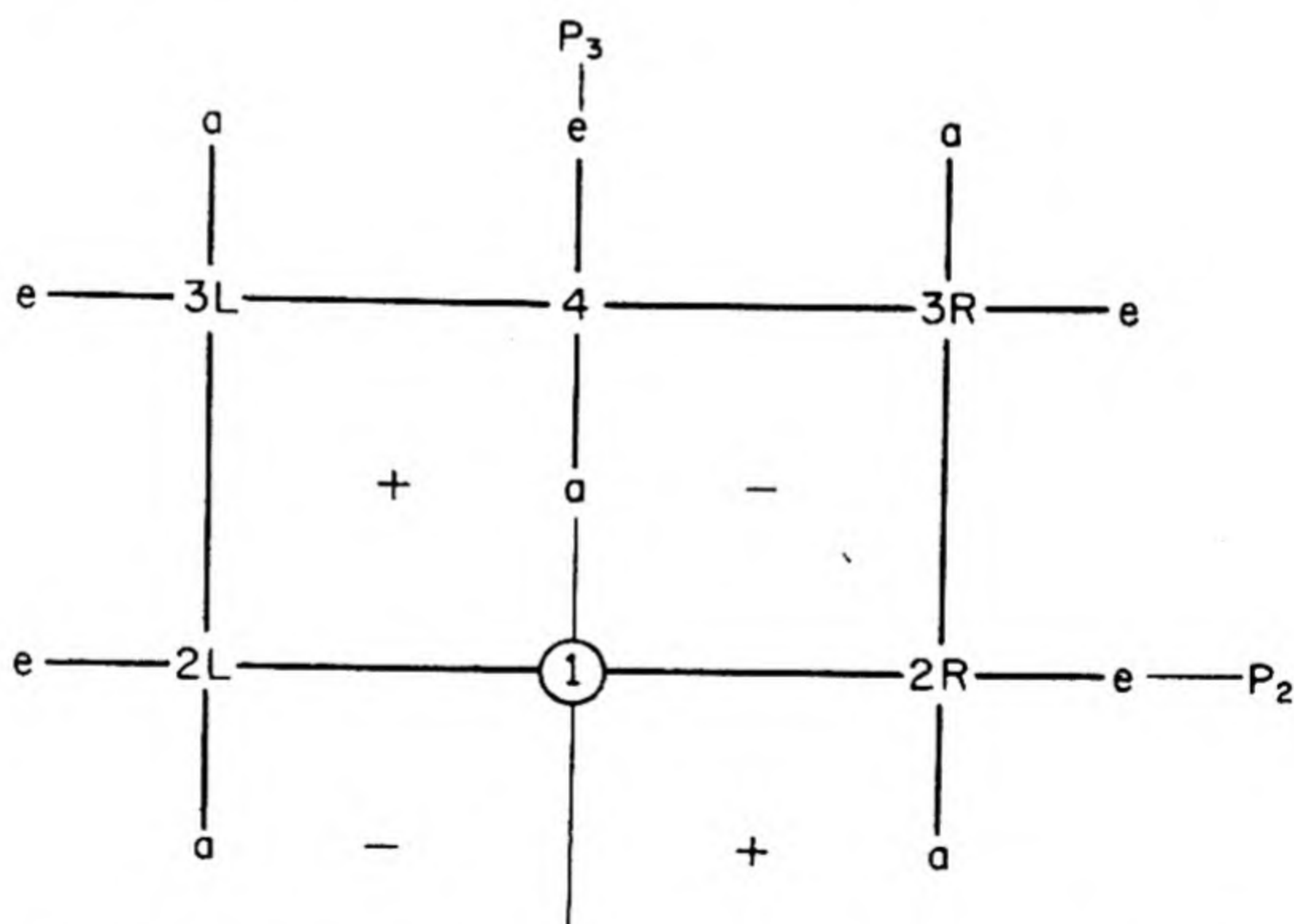
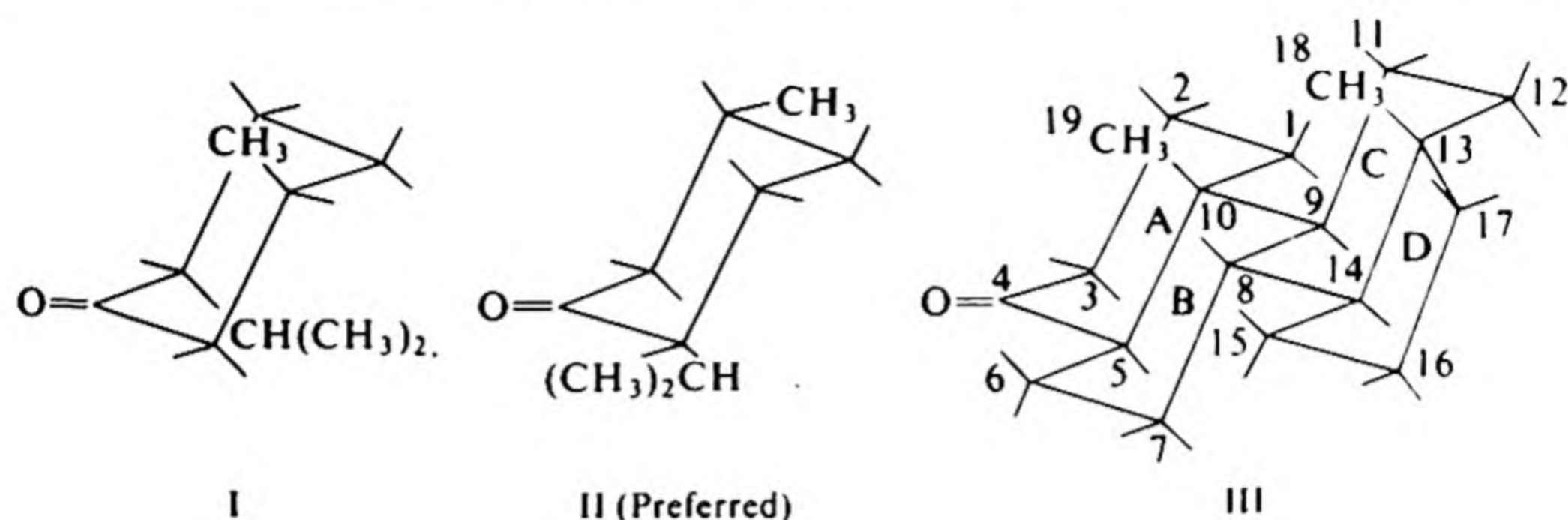


Fig. 32-3. Octant Diagram. The carbon which is doubly bonded to the oxygen in Fig. 32-2 is Carbon 1. The rearmost carbon in Fig. 32-2 is carbon 4.

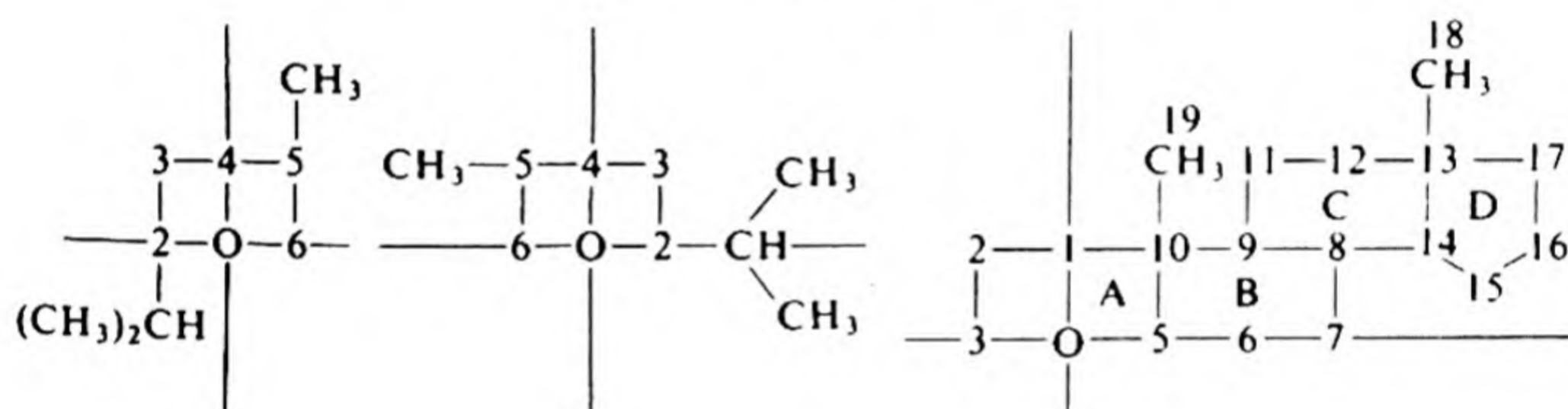
Hydrogen atoms are neglected. The number is italicized if the atom or group appears in the front (or near) octants.

Such an analysis is given in Table 32-1 for a relatively simple cyclohexanone derivative, menthone, I and II, and a steroid, 5α -androstan-4-

TABLE 32-1



OCTANT DIAGRAMS



SIGNIFICANT GROUPS



COTTON EFFECTS

	Predicted	Observed
I	-	+ 11
II (Pref.)	+	
III	--	- 94

one, III, both in dioxane solution. The Cotton effect is given, as customary, in amplitude units, $([\phi]_{\text{peak}} - [\phi]_{\text{trough}}) \times 10^{-2}$.

Note confirmation that the menthone conformer with equatorial equatorial *trans* methyl and isopropyl groups is preferred over the conformer in which both groups are axial. The fused ring system of the

steroid allows no such conformational freedom, hence its spatial arrangement is unambiguous.

C. Applicability of Optical Rotatory Dispersion

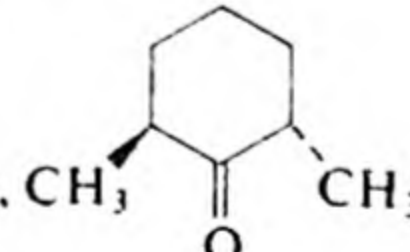
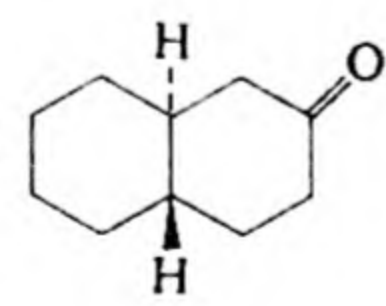
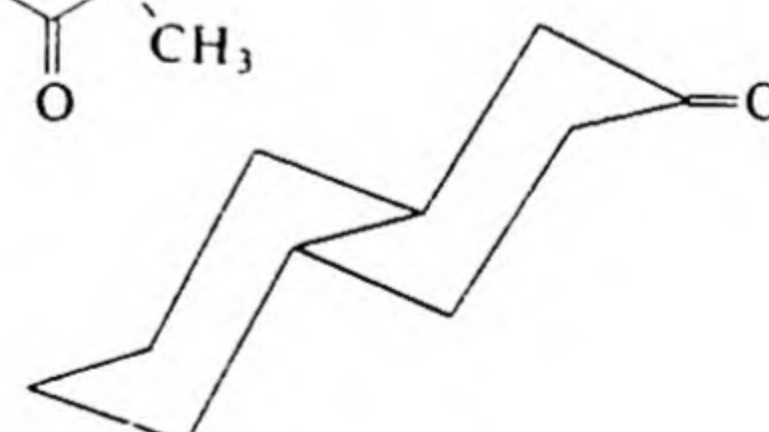
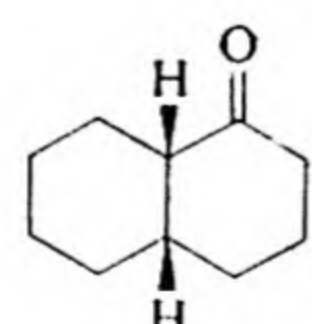
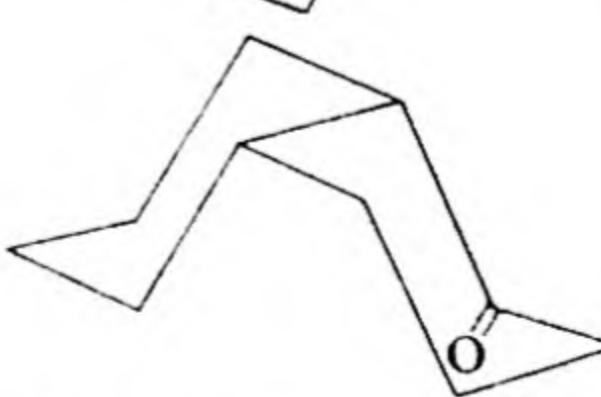
Thus far too few classes of compounds have been studied to arrive at any quantitative application of optical rotatory dispersion (ORD). Nevertheless, significant qualitative advances have been made which permit the assignment of absolute configurations to α -aminocarboxylic acids, saturated cyclic ketones (of 5- and 7-membered rings as well as 6-membered), especially α -halogenoketones, and α,β -unsaturated ketones.

SUPPLEMENTARY READINGS

- Djerassi, C., *Optical Rotatory Dispersion*, McGraw-Hill, New York, 1960.
 Eliel, E. L., *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962, Chapter 14.
 Klyne, W., "Optical Rotatory Dispersion" in R. A. Raphael, E. C. Taylor, and H. Wynberg, Eds., *Advances in Organic Chemistry, Methods and Results*, Vol. I, Interscience, New York, 1960.

QUESTIONS AND PROBLEMS

1. Differentiate between refractive dispersion and optical rotatory dispersion. In what way is ORD dependent on the former?
2. How do refractive dispersion and ORD differ in regard to their behavior in the vicinity of molecular absorption bands? Of what use is the behavior of ORD at these wavelengths?
3. Set up octant diagrams for the following compounds. Denote significant groups and predict the sign of the Cotton effect. If more than one chair conformation is involved, give the analysis for both.

- a. *trans*-2,6-dimethylcyclohexanone, 
- b. *trans*-2-decalone,  or 
- c. *cis*-1-decalone,  or 
- d. 5 α -androstan-3-one (see formula III, §32-5B)
- e. 5 α -androstan-2-one

33

Color and Spectra

33-1 SPECTRA AND ABSORPTION OF LIGHT

If electromagnetic energy provided continuously over a range of wavelengths is passed through excitable atoms or molecules, the spectrum of the transmitted energy shows that light is missing, or has been absorbed, at certain characteristic wavelengths. This spectrum is called an *absorption spectrum*.

33-2 MOLECULAR SPECTRA

A. Energy Changes in Molecules

The molecular characteristics in which energy changes are involved are electronic, vibrational, rotational, and translational (see Fig. 33-3). Molecular electronic changes and transformations in molecular motions each have characteristic ranges of wavelength in the electromagnetic spectrum (see Fig. 33-1 and §9-2A).

While a multitude of different electronic transitions is possible in a molecule, in general they involve elevation of electrons from bonding to antibonding orbitals. Excited acetylene and hydrogen cyanide molecules acquire different types of bond hybridization, leading to bent molecules with longer triple bond distances (Fig. 33-2).

The wavelengths of electronic transitions are usually in the region of ultraviolet or visible light (relatively high energies).

Energy transitions between vibrational states, rotational states, and translational states (Figs. 33-3 and 33-4) are based on a rather different principle. Nevertheless, like electronic energies, energies of molecular motions exhibit discrete levels. Light of energy $h\nu$, equal to the energy difference between vibrational energy levels, is absorbed in raising the molecular energy. Rotational and translational energy changes operate similarly.

Wavelengths of light associated with vibrational energy transitions are in the range of near infrared, that is, near to the visible spectrum (relatively low energies). Rotational energy transitions are associated with

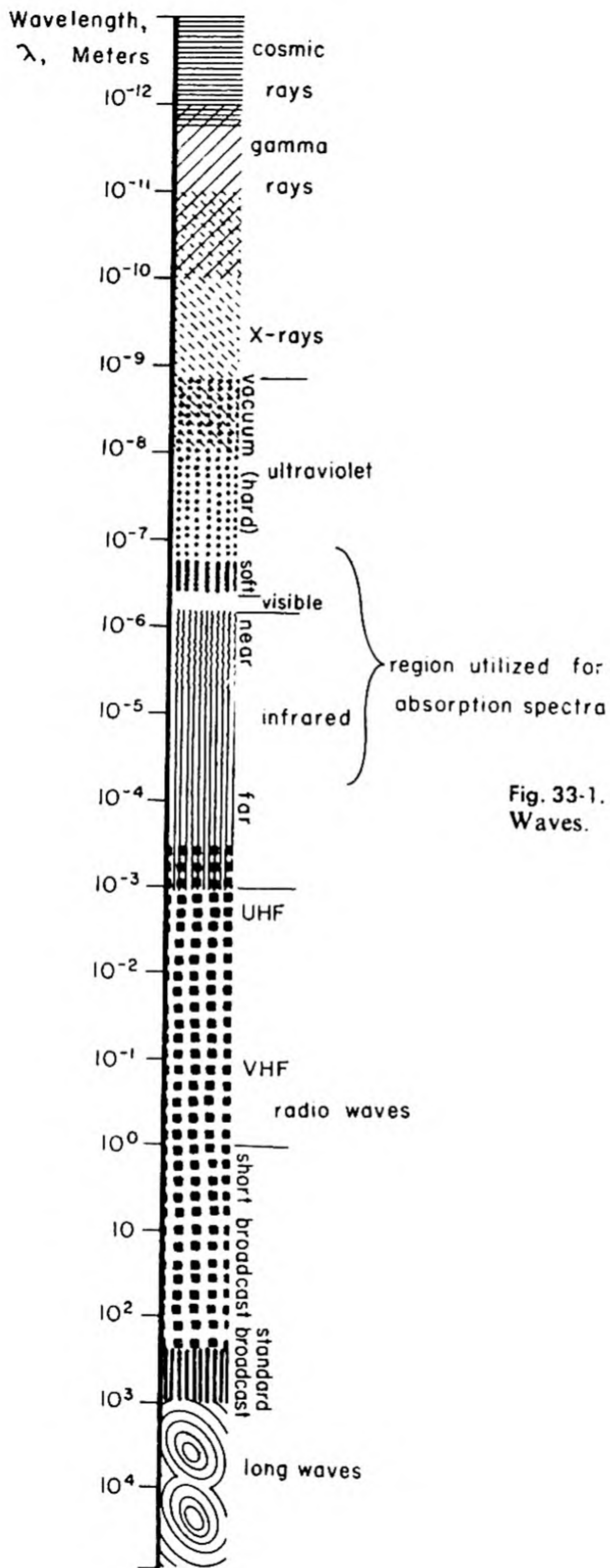


Fig. 33-1. Range of Electromagnetic Waves.

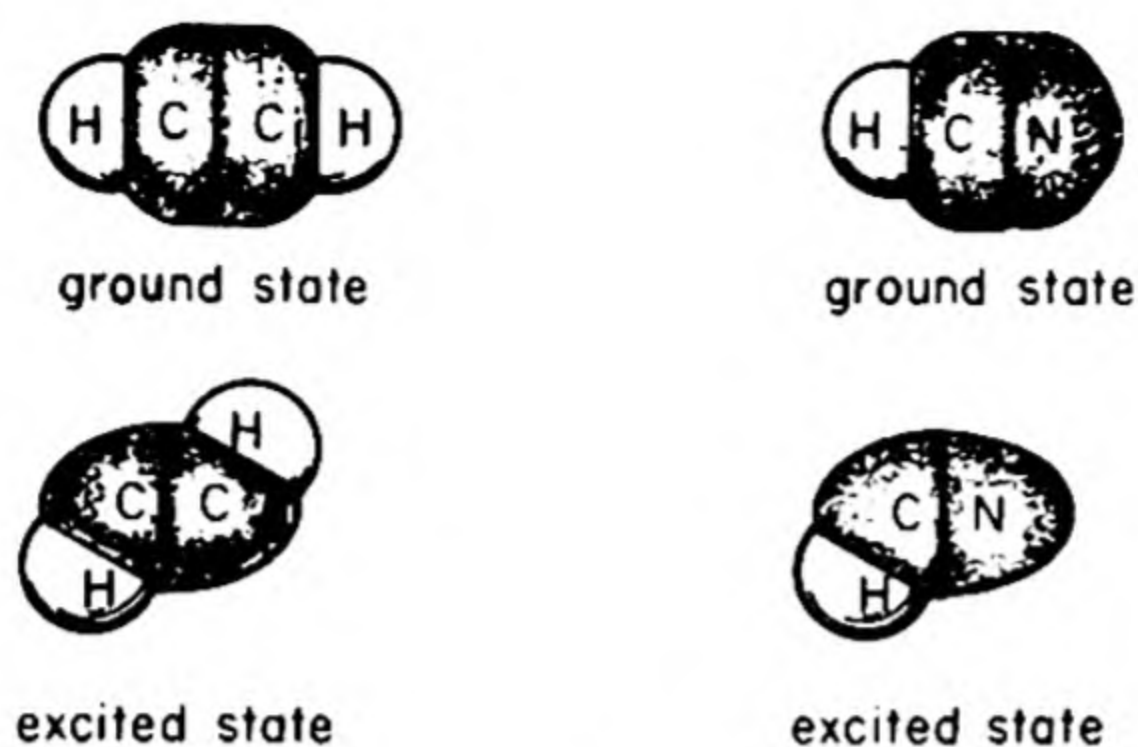


Fig. 33-2. Effects of Excitation on Triple Bonds.

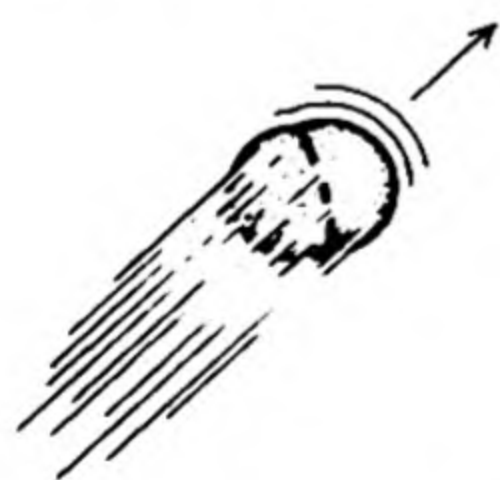


A. Vibrational Modes



B. Rotational Modes

Fig. 33-3. Types of Molecular Motions.



C. Translational Mode

wavelengths in the far infrared (quite low energies), that is, relatively far from the visible spectrum.

B. Using Spectra to Determine Structure

(1) *Ultraviolet and Visible Spectra.* Each energy transition, to recapitulate, is associated with a specific wavelength of light. However, molecular

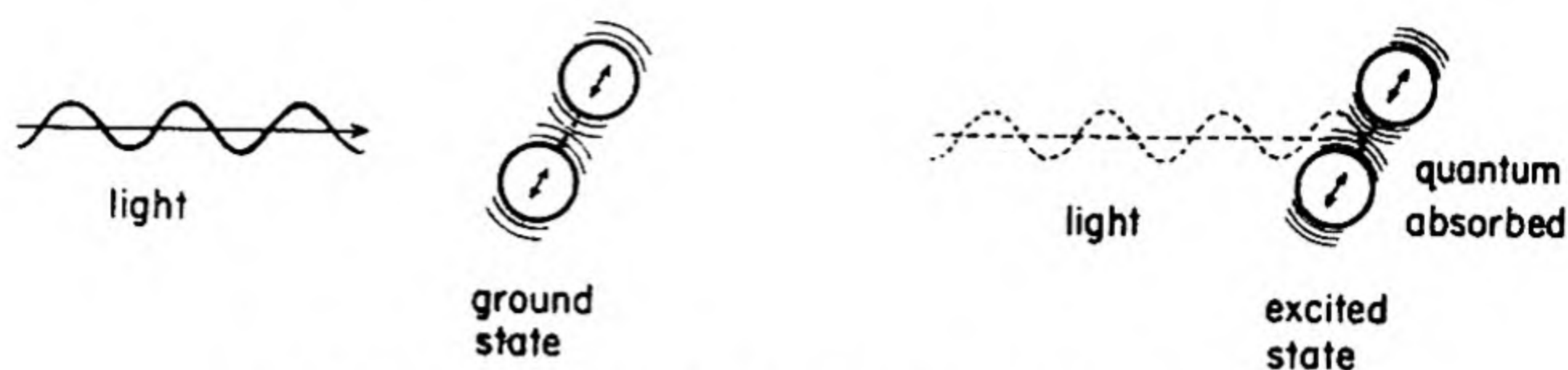
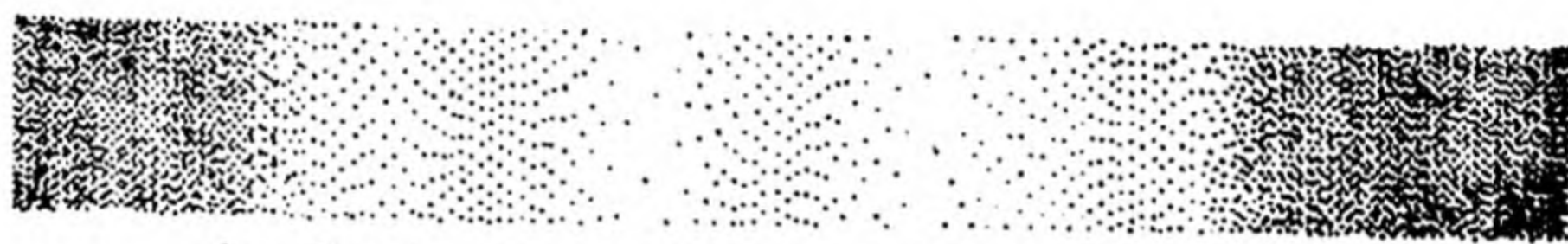


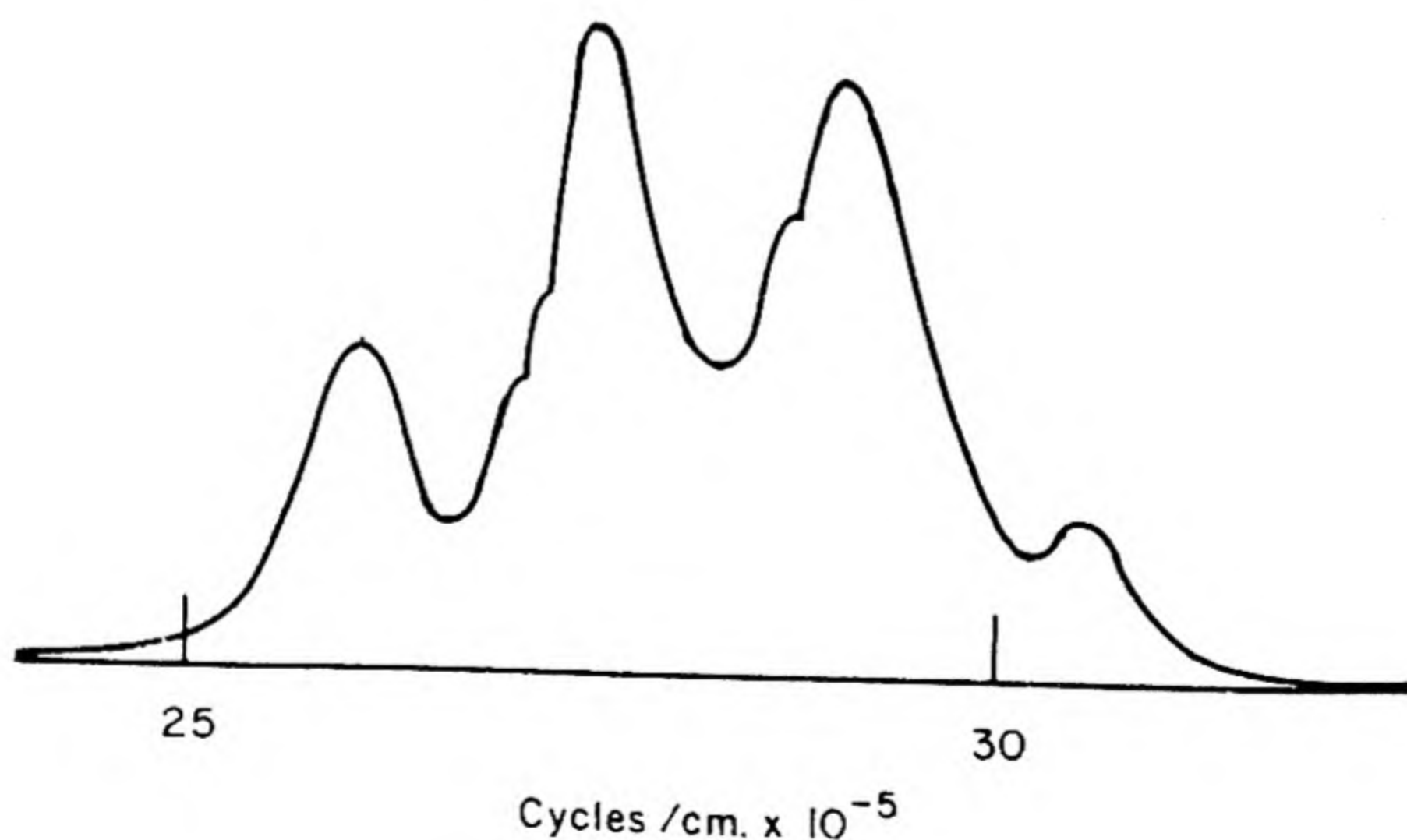
Fig. 33-4. Absorption of Light by Vibrational Transition.

spectra in the visible and ultraviolet regions are characteristically band spectra, not line spectra. This is due to very close spacing of spectral lines and to broadening of the lines by addition of vibrational and rotational transitions to the electronic transitions. Fig. 33-5 shows the relationship between band spectra and absorption curves.

A second characteristic of electronic molecular spectra is that the electronic environment has some influence on the electrons of each other



A. Band spectrum (photographic negative)



B. Absorption curve

Fig. 33-5. Correspondence Between Band Spectrum and Absorption Curve.

group. Consequently, the spectra are quite variable in relation to structural features except in the case of strong absorbers (chromophores, §33-2E) such as $C=O$, $C\equiv N$, or $C=C$.

Solvent-solute interactions introduce further energy terms that result in further broadening and blurring the absorption spectra. Solvent effects on the ultraviolet spectrum of benzene are shown in Fig. 33-6.

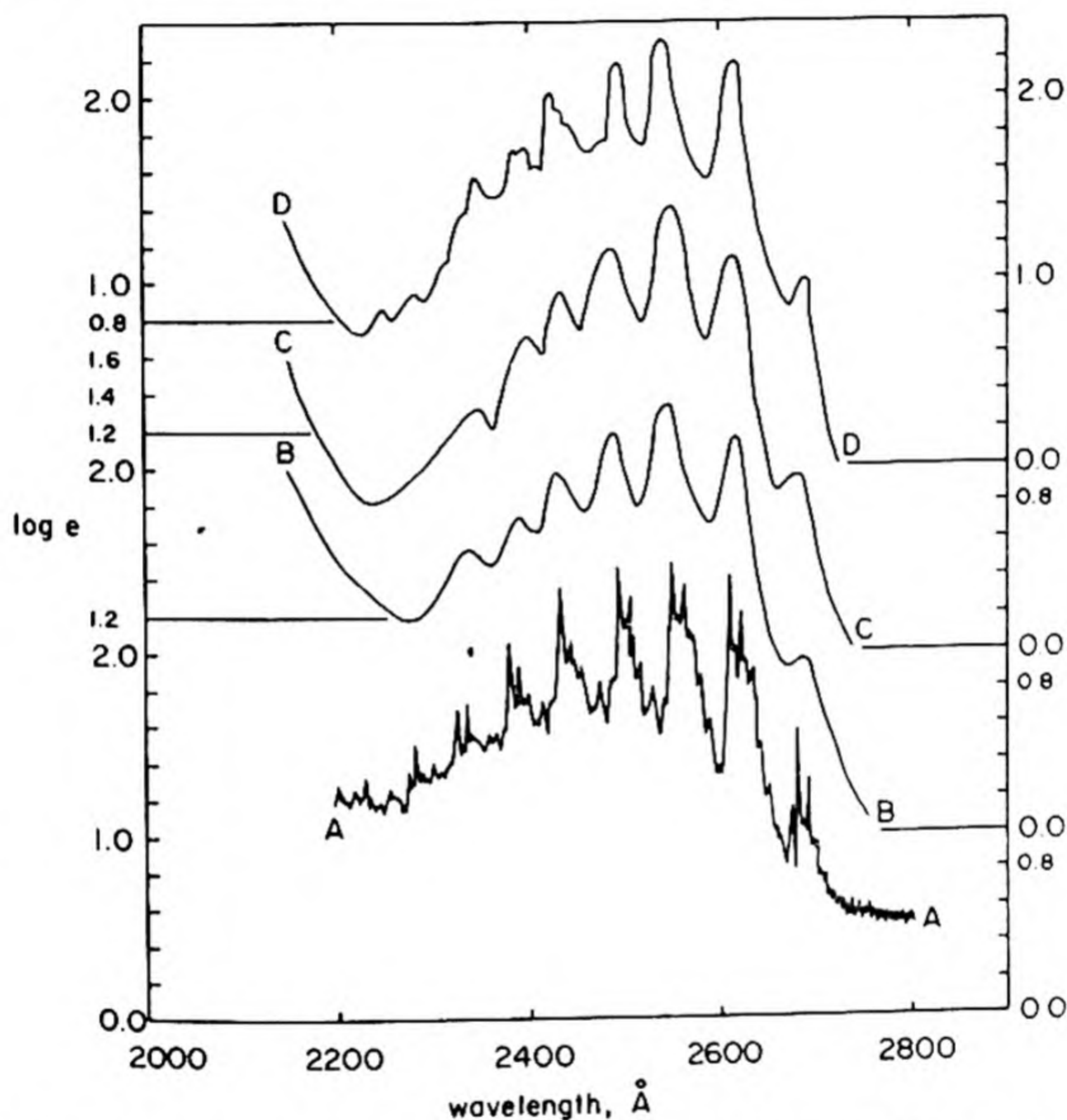


Fig. 33-6. Absorption Curves for Benzene, Pure and in Three Solvents. (A) Vapor phase, (B) In ethanol, (C) In heptane, (D) In cyclohexane.

Several terms used in quantitative description of spectra are important. *Absorption maxima* are wavelengths at which the most light is absorbed. They are also sometimes called *absorption peaks*. *Absorption minima* are wavelengths at which the most light is transmitted between maxima.

The law of light absorption (Beer-Lambert law) can be expressed in the form of either eq. (1) or (2).

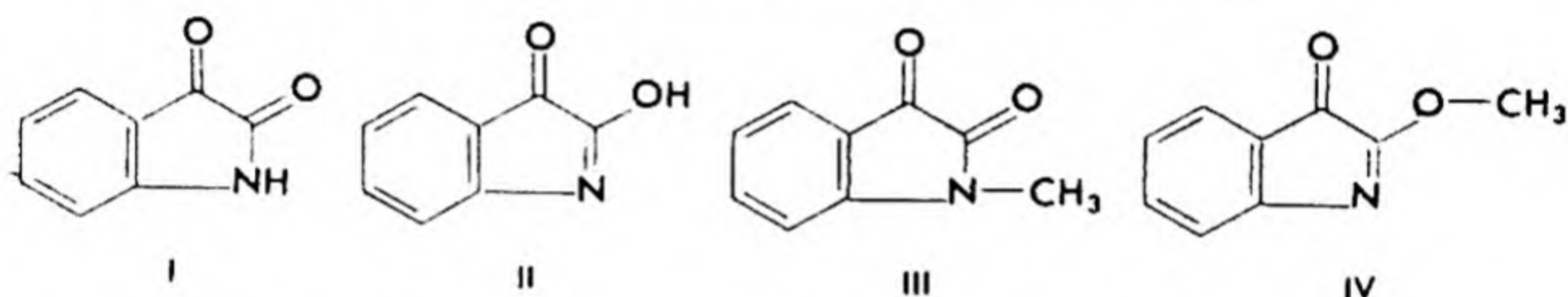
$$(1) \quad I = I_0 e^{-\epsilon c d}$$

$$(2) \quad \ln \frac{I}{I_0} = -acd$$

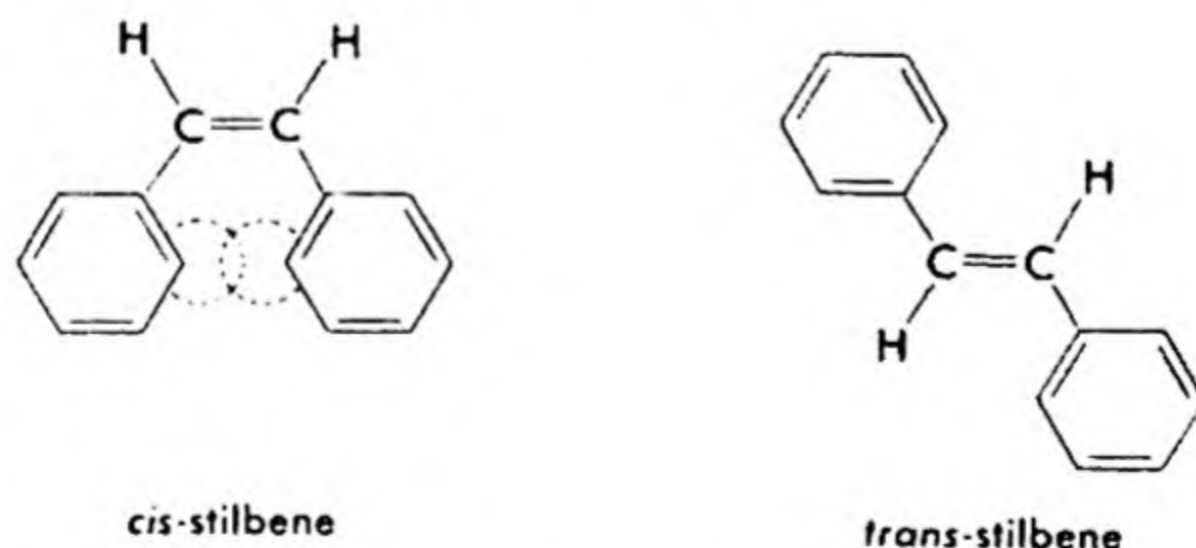
where I_0 is the intensity of incident light, I is the intensity of transmitted light. The concentration of solution is c , the thickness d . The term a (also given as e ; see Fig. 33-6) is the molecular extinction coefficient when c is given in molarity, d in centimeters. The molecular extinction coefficient is a constant for a substance at a given wavelength (provided there is no solvent interaction), but changes with change in wavelengths in a manner characteristic of the substance. This is the value plotted to give the usual absorption curve.

While absorption spectra are unique properties of substances, closely related or homologous compounds may have significantly similar spectra. A large number of structure determinations depend on this fact. A few of the more outstanding types of information gleaned are summarized below.

Isatin might have either tautomeric structure, I or II. The methyl derivatives, III and IV, are both available; their spectra are different. The absorption curve for isatin corresponds more closely to that of the *N*-methyl derivative (III); hence, isatin exists largely as tautomer I.



Resonance in stilbene-like systems depends on the coplanarity of the entire conjugated system. Where steric hindrance forces components of the system out of the plane, resonance is inhibited and absorption maxima are less intense and occur at shorter wavelengths.



Thus, *cis*-stilbene absorbs at shorter wavelengths than *trans*-stilbene, because the *ortho* hydrogen atoms interfere with coplanarity in the former.

(2) *Infrared Spectra.* At first glance, infrared spectra appear to be more complex than ultraviolet spectra. This apparent complexity is due to much better resolution of a simpler spectrum. Infrared lacks the elec-

tronic energy transitions. Medium near infrared has vibrational transitions overlaid by rotational transitions.

Since infrared spectra depend on molecular motions, they are subject to masses of component parts. Very seldom do complex molecules strike vibrational modes encompassing the entire molecule. As on a charm bracelet, each pendant, or group, of the molecule joggles separately in its own peculiar frequency. Hence, absorption maxima in infrared are characteristic of specific groups (see Figs. 33-7, 9-7, and 9-8).

Because of its group characteristic frequencies, an infrared spectrum is a powerful tool for structural analysis. Not only can the types of groups be deduced from the spectrum, but their number can often be inferred from the intensity of their absorption maxima. Furthermore, although the molecule as a whole does not dominate the nature of the spectrum, it has an influence, so that positional isomers, *cis-trans* isomers, and the like can be readily distinguished. Infrared absorption is a much more powerful tool than ultraviolet absorption in this respect. As a quantitative tool, IR has been used to determine the proportions of components in a mixture within a few per cent.

As a tool in reaction studies, IR analysis is invaluable for following the disappearance of reagents and formation of products. Not only can the overall production of compounds be followed, but their nature and proportions ascertained. For example, the proportions of *cis*-1,4, *trans*-1,4 and 1,2-additions in polymerization of butadiene can be determined by IR. The technique is simply that of determining the heights of different peaks characteristic of the three forms and solving three simultaneous proportionality equations.

C. Effect of Conjugation on Electronic Energy Transitions

If conjugated unsaturated systems did not interact, the energy levels of all double bonds would be the same as those for ethylene (see Kekule benzene vs. resonance benzene, Fig. 7-3). The lowest possible electronic transition would then be the elevation of a π electron to the π^* (anti-bonding) level (Fig. 33-8). Multiplicity of double bonds would simply increase the extinction coefficient (the intensity of absorption), as is found in systems of isolated double bonds.

Resonance, however, changes the orbital situation. The lowest energy π orbital in an aromatic system has a much lower energy than an olefinic π orbital. This aromatic orbital holds two electrons. The remaining electrons of the conjugated system must go into higher energy levels, some of which may also be lower than the levels of ethylene. As the system becomes more complex, and more electron pairs become involved in resonance, the difference in energy between the highest filled π orbitals of the molecule and the lowest energy empty π^* orbitals becomes smaller (see

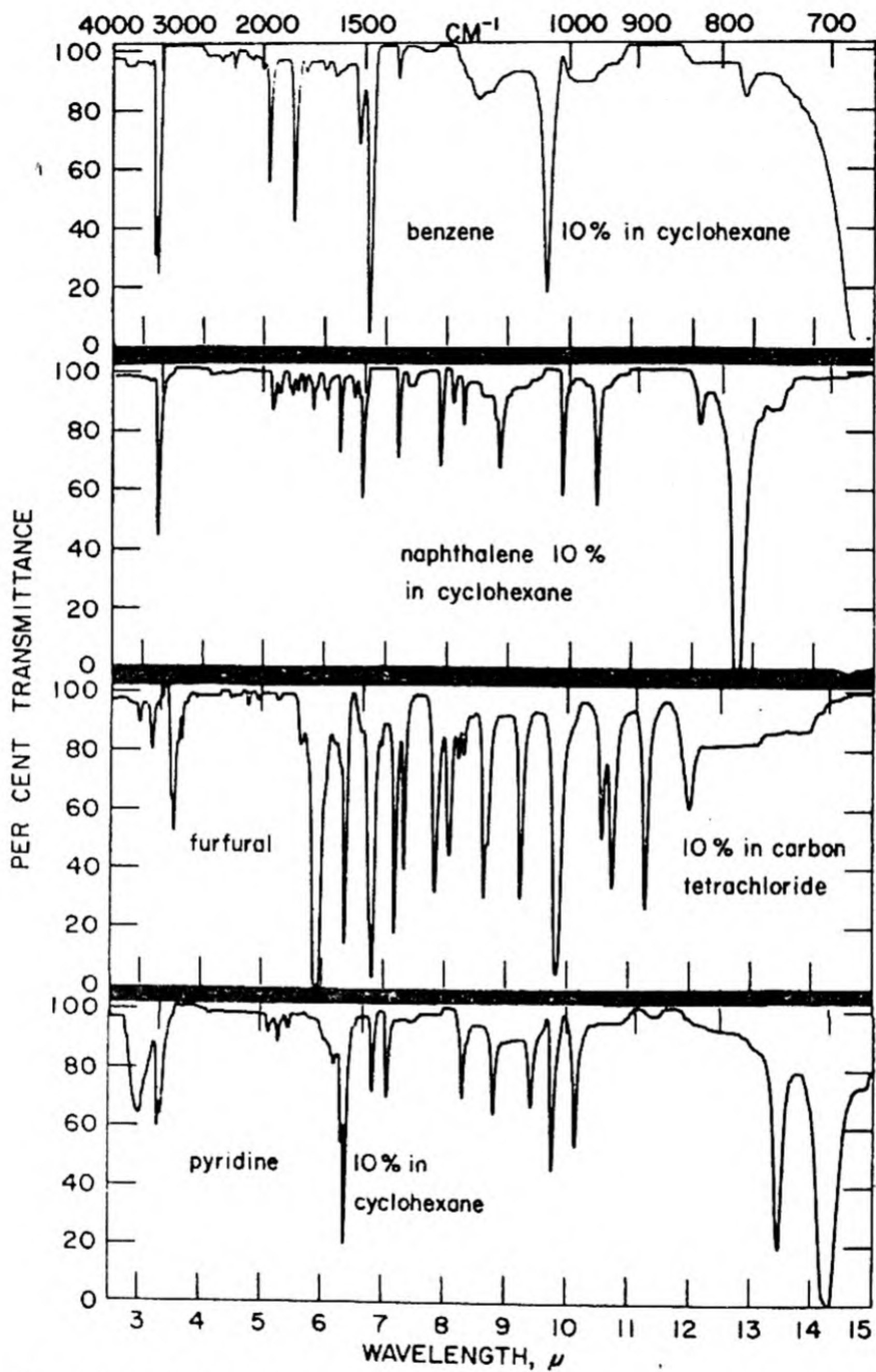


Fig. 33-7. Infrared Spectra of Representative Compounds in Cyclohexane or Carbon Tetrachloride.

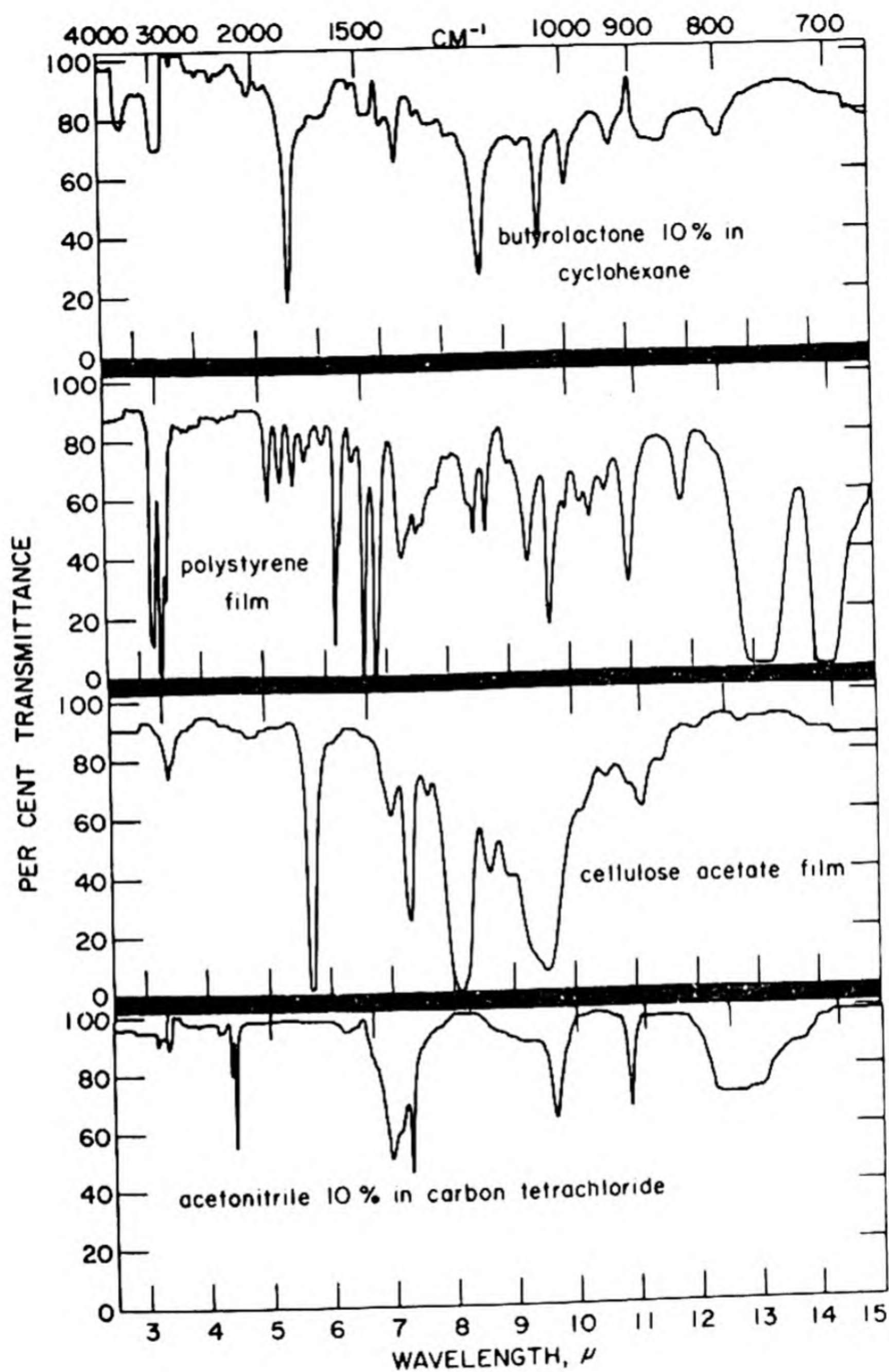


Fig. 33-7. (Continued)

Fig. 33-8). The result is that the more extensive the conjugation, the closer are the highest filled π orbitals to the lowest empty π^* orbitals. Consequently, conjugation moves the range of absorption toward longer wavelengths. The more extensive the conjugation, the greater this *bathochromic* shift.

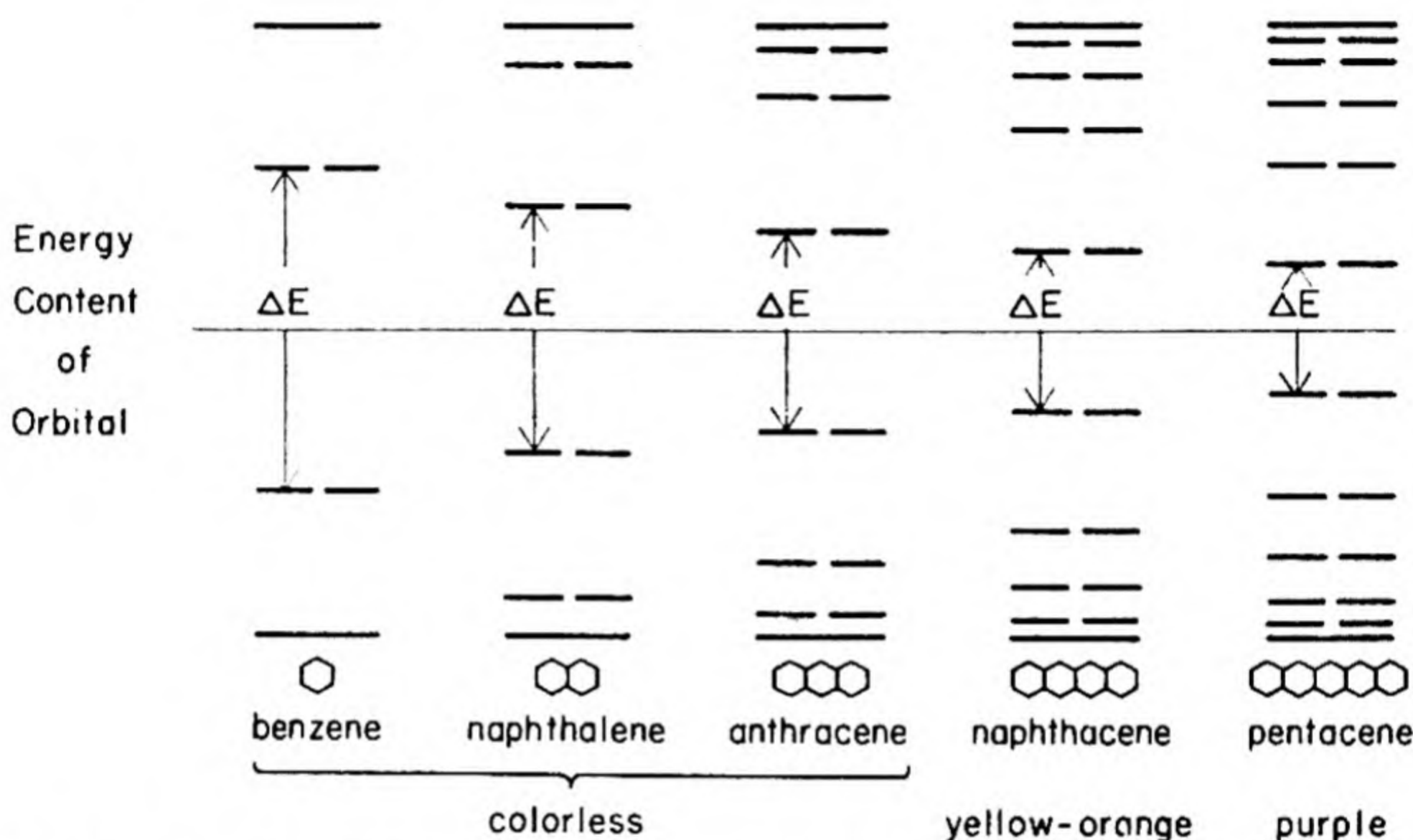
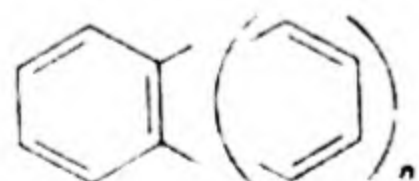


Fig. 33-8. Effect of Complexity of Resonance System on Energy Transitions from Highest Occupied to Lowest Unoccupied Levels.

The effect of lengthening a conjugated system on the range of wavelengths absorbed is strikingly illustrated in the series of compounds $C_6H_5-(CH=CH)_n-C_6H_5$ in benzene solution (Fig. 33-9) and the series



(Fig. 33-8). From the orbital energy levels given in

Fig. 33-8, it is apparent that the energy required to raise an electron from the highest bonding orbital to the lowest antibonding orbital decreases as n increases. While other factors enter into the ΔE for the first excitation, to a first approximation, this transition energy is simply the difference in energies between the highest occupied level and the lowest unoccupied level. Other series have similar energy considerations, though the orbitals may be more complex. Since $\Delta E = h\nu = hc/\lambda$, in which h is Planck's constant, ν the frequency, λ the wavelength, and c the velocity of light, it is apparent that ΔE is inversely proportional to the wavelength of light absorbed.

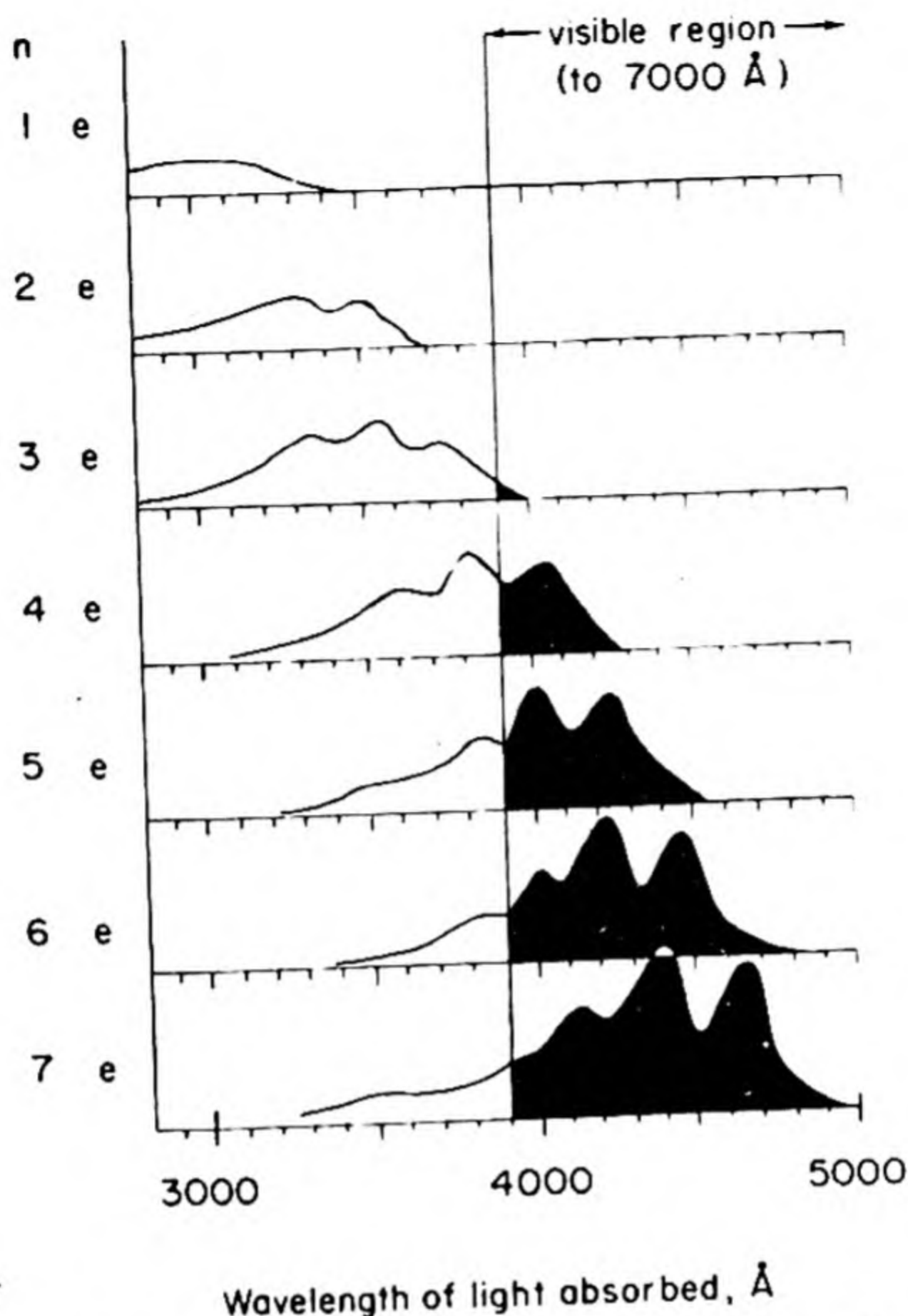
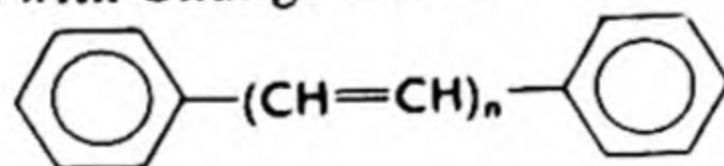


Fig. 33-9. Change of Wavelength and Extinction Coefficient with Change of n in



D. Production of Visible Color

Color is a physiological sensation associated both with wavelengths of light striking the retina and with relative intensities of long and short waves of light striking the retina regardless of their actual wavelengths. An arbitrary classification of discrete colors in order from the short to long wavelengths is violet, blue, green, yellow, orange, and red. Color can be observed when a source emits light of a certain wavelength in the visible region. For example, when sodium vapor is heated, yellow light is emitted. Such emission is due to falling of the electrons which have been raised thermally to excited states from the higher to lower energy levels. Certain excited molecules or molecular fragments may also give emission

spectra, though such an effect is often difficult to produce without decomposition of the molecule.

An alternative process for color observation is the absorption of a short band of wavelengths from white light. A visual sensation of color *complementary* to the color associated with emission in the absorbed region results. Table 33-1 shows the relationship between the color associated with emitted light of a given region and that associated with absorption of light in the same region. Absorption of light invisible to the eye has no effect on the observed color.

TABLE 33-1. Emission and Absorption Color Relationships

Wavelengths, Å Emitted or Absorbed	Color Seen upon Emission	Color Seen upon Absorption
4100	violet	yellow
4600	blue	orange
5400	green	red
5800	yellow	violet
6100	orange	blue
7000	red	green

E. Chromophores, Auxochromes, and Hypsochromes

An early theory of dyes first formulated by Otto Witt (1876) provided the foundation for an understanding of the molecular basis of color. According to the Witt color theory and its extensions, a dye is made up of two essential kinds of parts, *chromophores* and *auxochromes*. Chromophores (Gk., *khroma*, color and *phoros*, carrier) are unsaturated groups, the presence of at least one of which is essential to produce color in a compound. Auxochromes (Gk., *auxanein*, to increase) are groups which deepen color when chromophores are present. Three kinds are classified, those which are electron sources, those which are electron sinks, and those which may be either. Examples of chromophores and auxochromes are given in Tables 33-2 and 33-3.

Like many other primitive theories, the Witt theory has been replaced by modern electronic theories. As was pointed out before, it is resonance stabilization of excited states that is responsible for absorption in the visible region.

The effects of chromophores and auxochromes on absorption spectra are illustrated in Fig. 33-10. Here the benzene ring may be considered to be a chromophore, while the auxochromes, the amino group and the nitro group, are, respectively, an electron source and an electron sink. When these are conjugated, the longer resonance system decreases the energy

TABLE 33-2. Chromophores

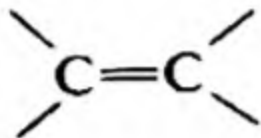
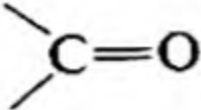
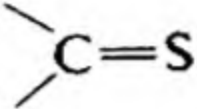

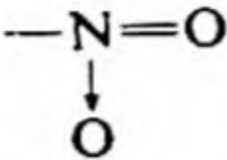
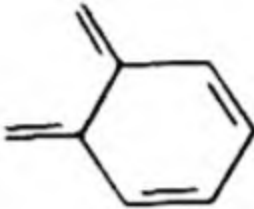
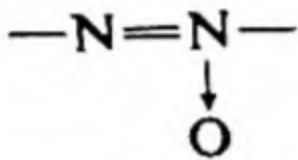
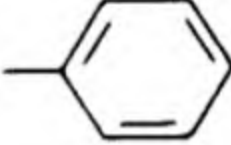
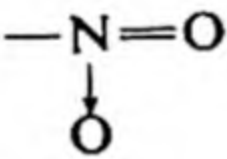
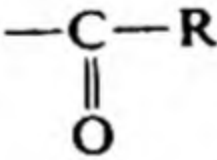
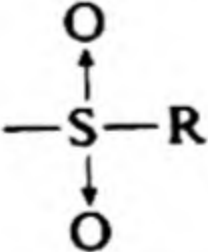
		
$-\text{CH}=\text{N}-$	$-\text{N}=\text{O}$	
$-\text{N}=\text{N}-$		
		

TABLE 33-3. Auxochromes

Electron Sources	Electron Sinks	Ambielectronic
$-\text{OH}$	$-\text{N}=\text{O}$	
$-\text{OR}$		$-\text{CH}=\text{CH}_2$
$-\text{NH}_2$		$-\text{N}=\text{N}-\text{R}$
$-\text{NHR}$	$-\text{C}\equiv\text{N}$	
$-\text{NR}_2$		

gap of the ground state-excited state transitions, with visible color production as a result. All of these groups are *bathochromes*, groups which lengthen wavelengths of absorption maxima in molecules in which they occur.

Hypsochromes are groups which diminish resonance, often by forcing π orbitals out of coplanarity. Examples are alkyl groups on benzene rings *ortho* to adjacent rings or chains, where they force such groups into positions unfavorable to transmission of resonance across the molecule.

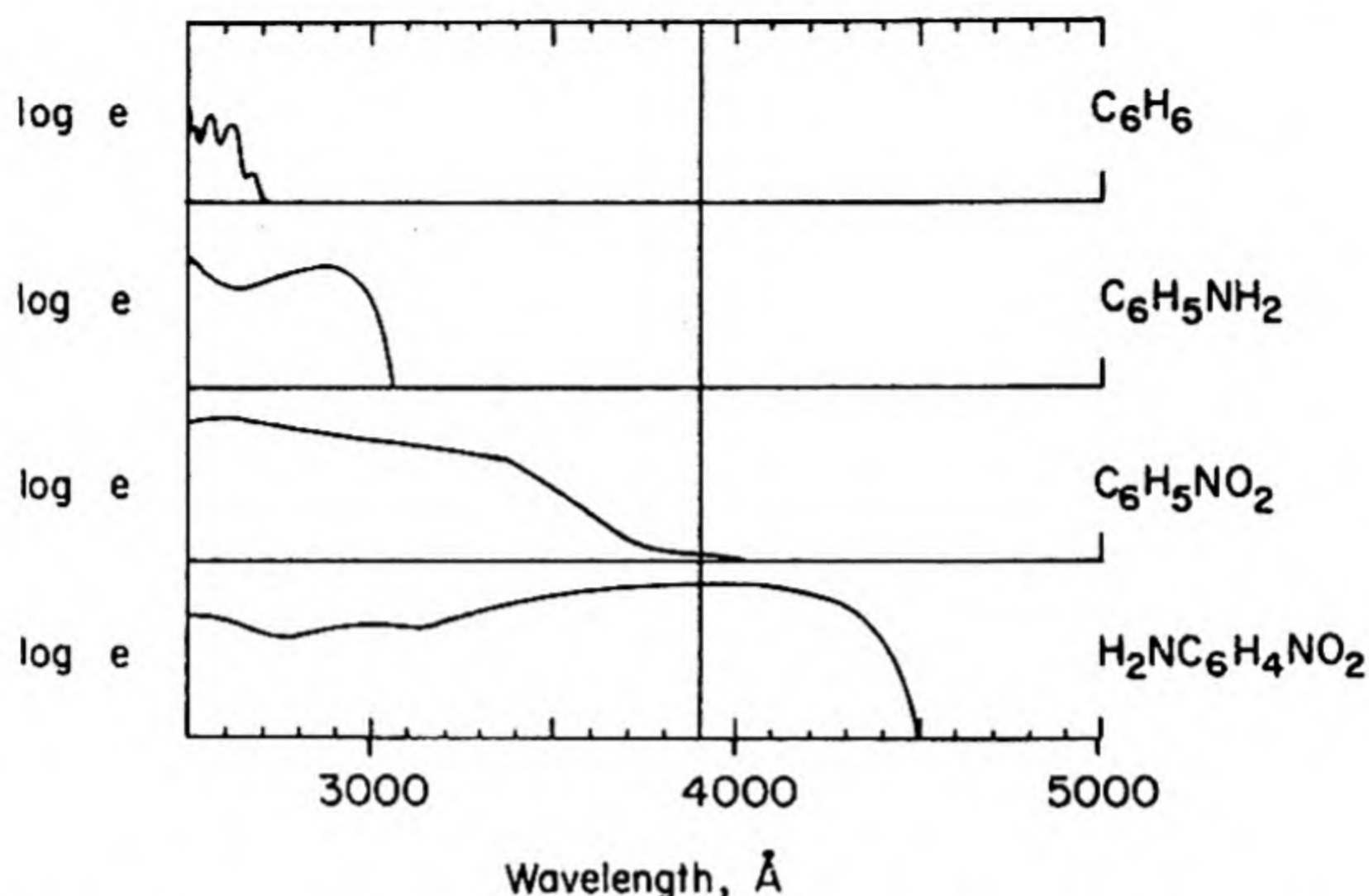


Fig. 33-10. Absorption Spectra of Benzene, Aniline, Nitrobenzene, and *p*-Nitroaniline.

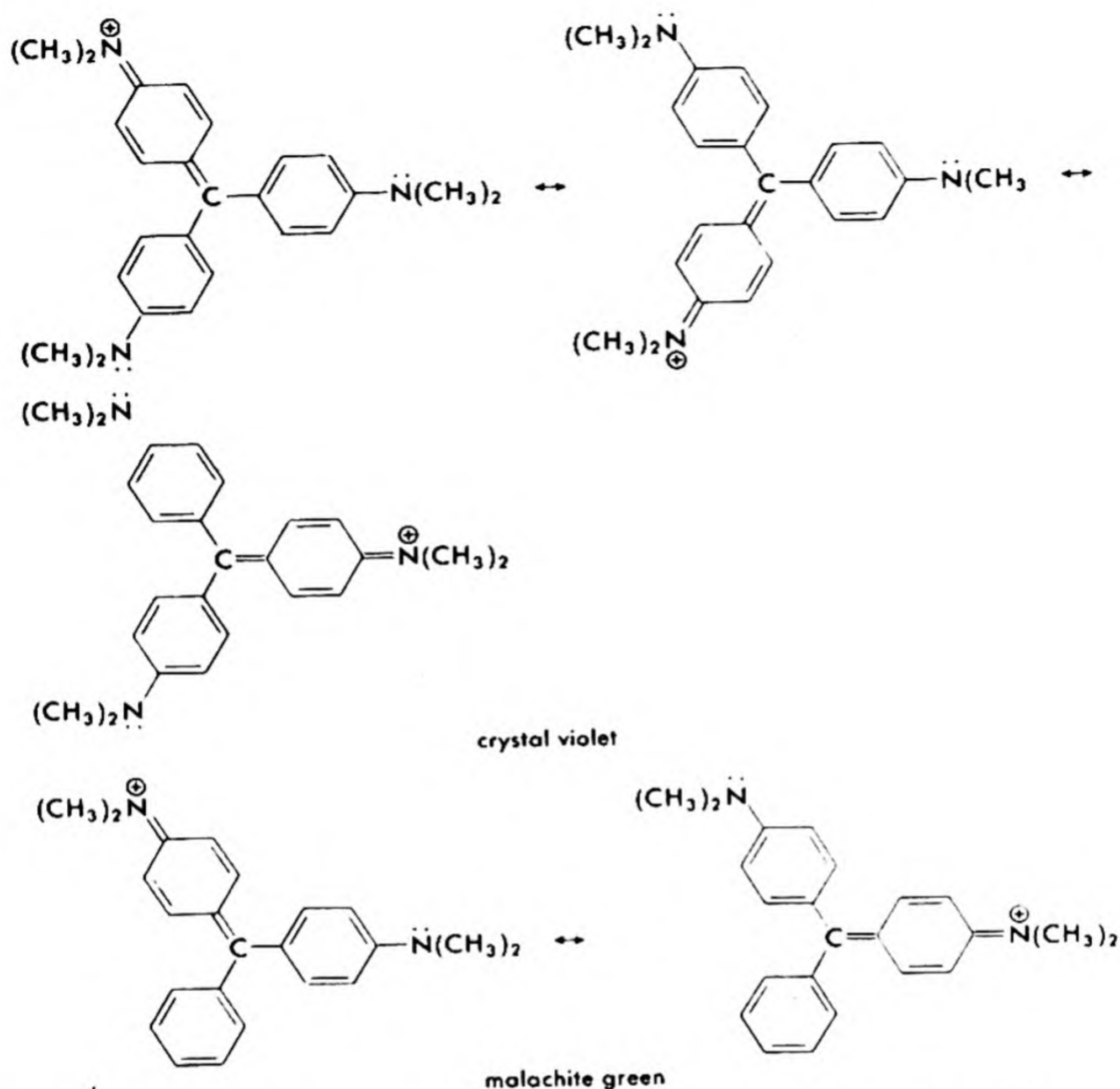
33-3 DYES AND DYEING

A dye is a material that (a) absorbs strongly in the visible region and (b) adheres to a surface by virtue of chemical or physical attraction between groups on the dye and groups on the dyed substance. A classified list of important dye types is given in Table 33-4. The dyes are classified according to their chromophores. The mesomeric systems are emphasized by the use of bold type.

The effects of the extent of resonance on energy transitions are colorfully illustrated in dyes. Crystal violet, which has twelve identical canonical structures (including Kekule structures for the aromatic rings), absorbs light farther into the visible spectrum than malachite green, which has only eight major contributing structures.

In addition to these lower-energy contributing structures, a number of higher-energy carbonium forms make minor contributions to charge delocalization (see the triphenylcarbonium ion, §12-1B(4)).

Possibly even more interesting than dyes from the viewpoint of energy transitions is a new class of compounds called *optical bleaches*. This is but one of many types of fluorescent compounds. *Fluorescence* is the ability of a compound to absorb light of high energy (UV) and re-emit the light in short, lower energy transitions in the visible range. Actually, many common compounds fluoresce, among them anthracene, fluorene, and fluorescein (whence the names of the last two). The primary characteristics of an optical bleach are that it be colorless and that it emit blue light. The practical value of the latter is to offset blue absorption (yellowing) in textile fabrics through accumulated soil and deterioration



of certain fabric components. Thus, clothing washed with a detergent mixture containing an optical bleach becomes "whiter than white."

Typical energy transitions involved in fluorescence are shown in Fig. 33-11, p. 658. Each electronic state has several associated vibrational levels. A resting molecule will generally be in the lowest vibrational level of the ground electronic state. Absorption of light, A , promotes the molecule to one of the *higher* vibrational levels of the first excited state. The reason is shown in Fig. 33-11 inset. The atoms of the molecule do not have time to move from their optimum distances in the ground state, G , to those of the excited state, E ; hence the excited molecule automatically finds itself in a higher vibrational level, at v_2 . This super-excited molecule loses the excess vibrational energy in collisions with other molecules, the wavy arrow C' . Some molecules can also lose the energy, F , by collisions, but others emit electromagnetic energy, F , before they can collide (about 10^{-8} sec.). Again, the molecule finds itself in a higher vibrational level,

TABLE 33-4. Dyes Classified According to Chromophores

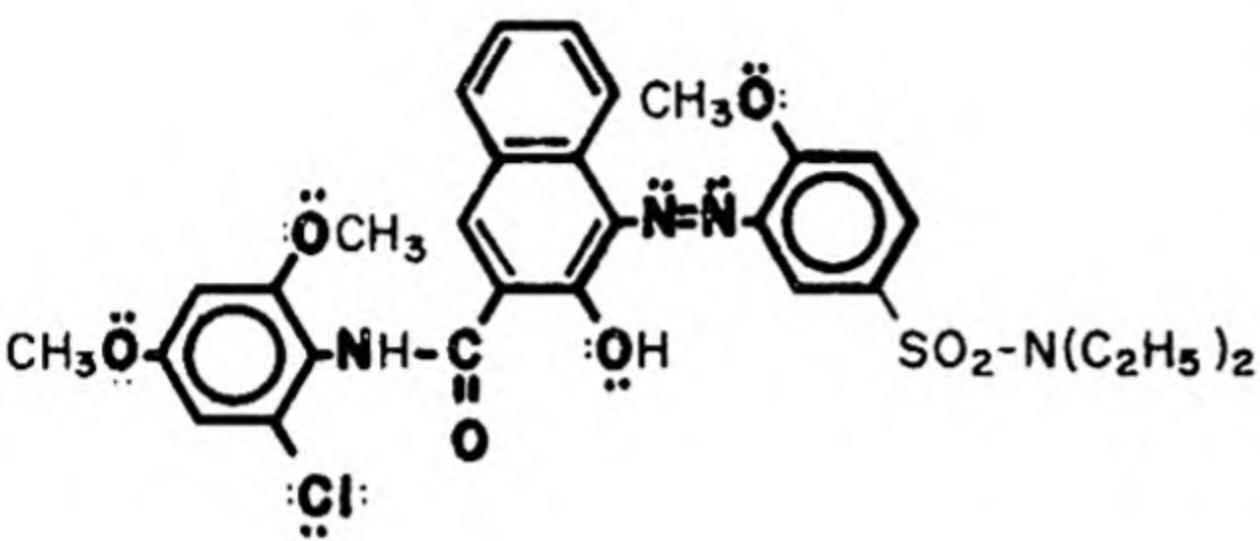
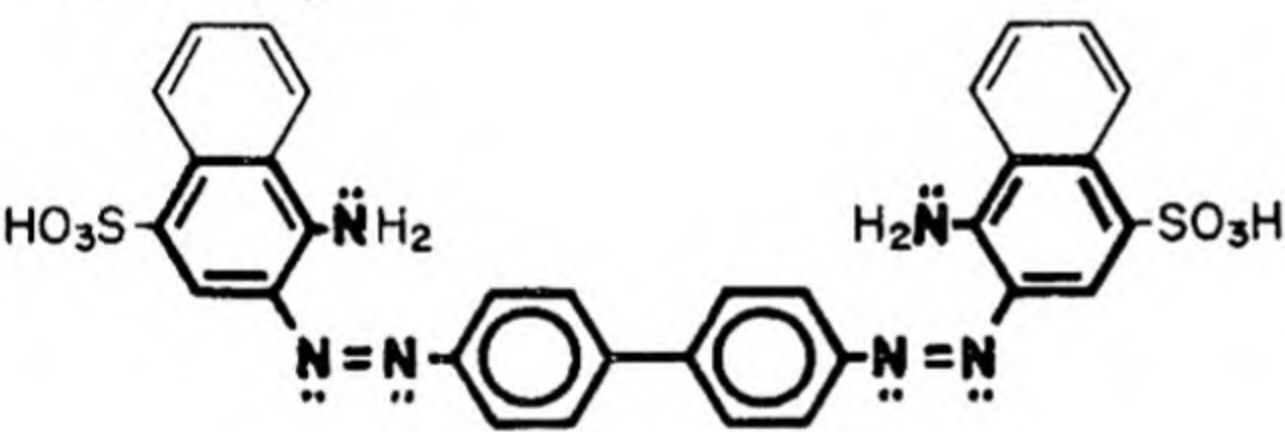
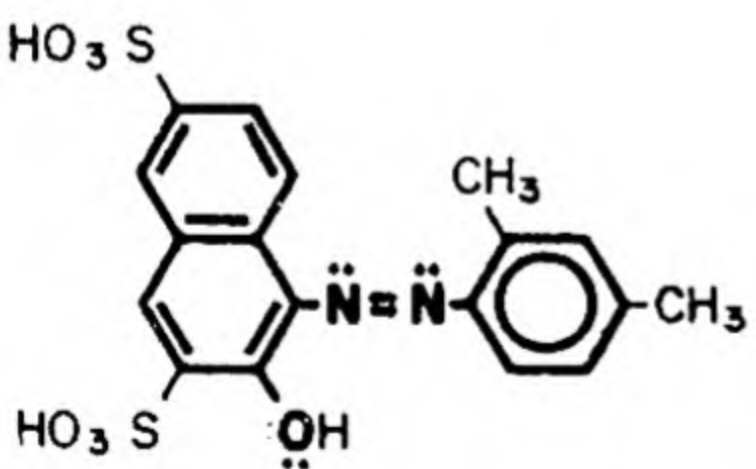
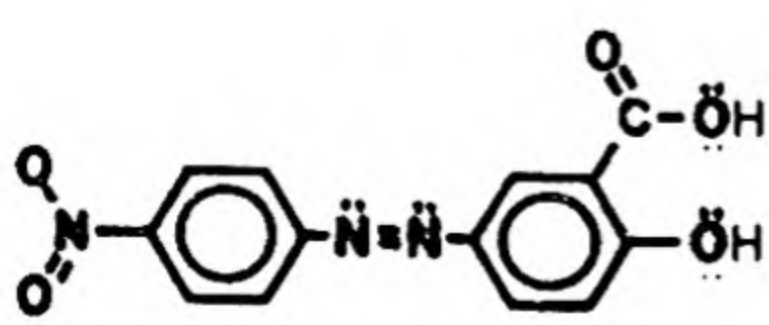
Formula	Name and Comments
1. Azo dyes	
a. Azoic dyes	
	<p>Naphthol AS-ITR + Fast Red ITR Base. An Azoic dye is an ingrain dye of the azo type, characterized by lack of hydrophilic groups, and containing an aryl amido group. An ingrain (or developed) dye is a dye formed by coupling directly on a fabric. Separate solutions of the diazonium salt and the coupler are required.</p>
b. Acid dyes	
	<p>Congo Red An acid dye is any dyestuff that has acid functions, such as carboxyl groups and sulfo groups.</p>
	<p>Ponceau Red 2 R A lake is a dyestuff adsorbed on an insoluble metal compound. A pigment is a colored material which is embedded in the material it colors.</p>
	<p>Alizarin Yellow R Also used as an indicator.</p>

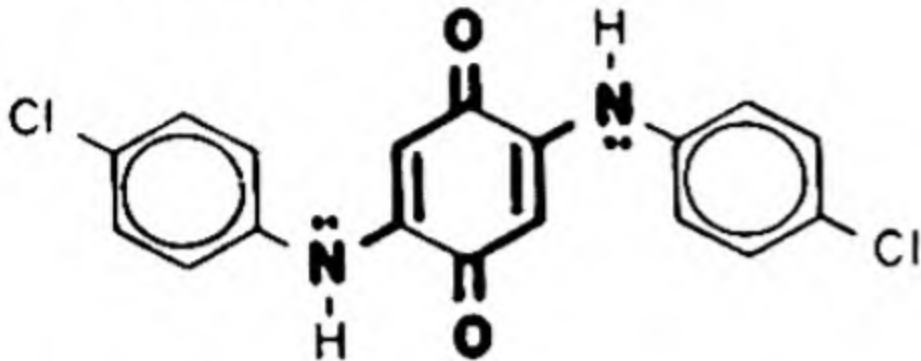
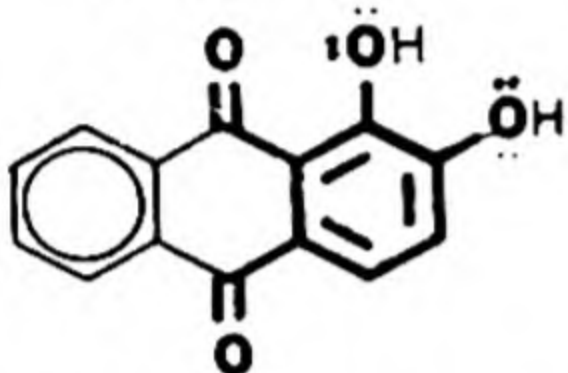
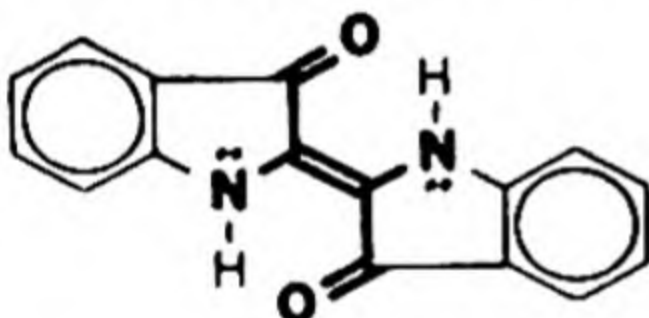
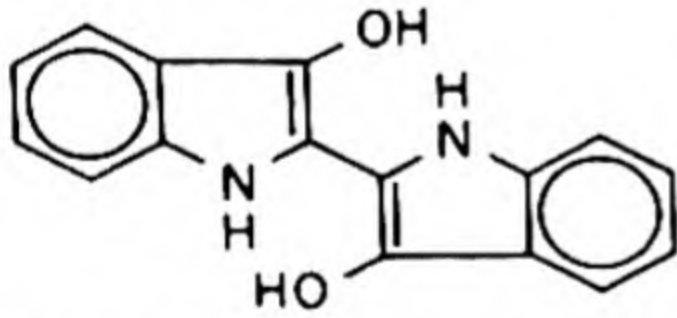
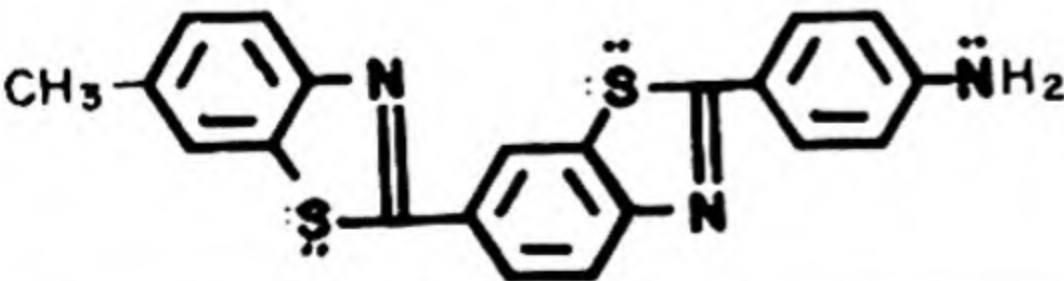
TABLE 33-4 (Continued)

Formula	Name and Comments
2. Triphenylmethane dyes	
a. Basic dyes	
	<p>Malachite Green A basic dye is any dyestuff having basic functional groups, such as amino, guanidino, amidino.</p>
	<p>Fuchsin, Magenta, Rosaniline</p>
b. Acid dyes	
	<p>Chrome Violet CG</p>
c. Phthalein dyes	
	<p>Fluorescein</p>

TABLE 33-4 (Continued)

Formula	Name and Comments
	Eosin
<p>3. Azine dyes</p> <p>a. Oxazines</p>	
	Capri Blue
<p>b. Acridines</p>	
	Acridine Yellow G
<p>c. Phenazines (safronines)</p>	
	Mauveine
<p>4. Nitro dyes</p>	
	Amido Yellow E

TABLE 33-4 (Continued)

Formula	Name and Comments
5. Quinone dyes a. Simple quinones	
	Helindon Yellow CG
b. Alizarins	
	Alizarin
6. Miscellaneous types a. Indigoid dyes (vat dyes)	
 <p data-bbox="282 1751 564 1791">indigo (blue)</p>	<p data-bbox="1336 1690 1479 1730">Indigo</p> <p data-bbox="1336 1742 1939 2011">A vat dye is a dye applied as a solution of colorless, reduced form (leuco base), which then air oxidizes on the fabric.</p>
 <p data-bbox="171 2173 707 2212">leucoindigo (hydroindigo)</p>	
b. Sulfur dyes (vat dyes)	
	Primuline

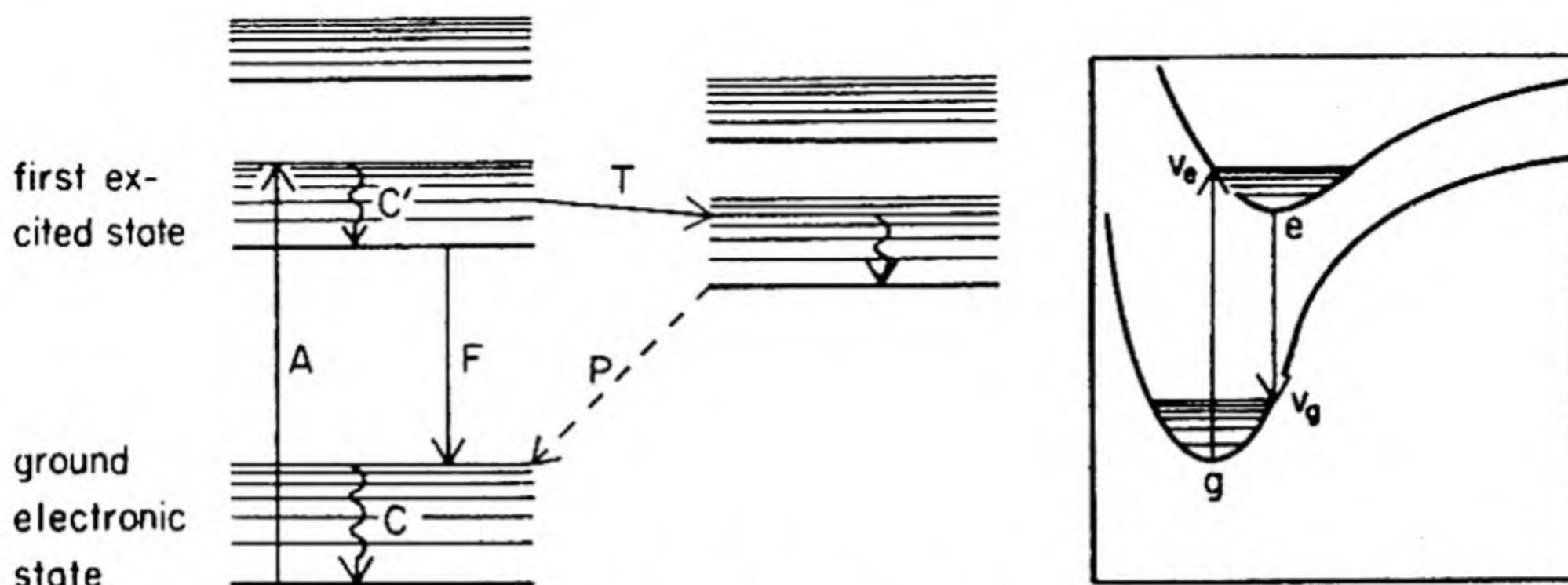


Fig. 33-11. Energy Transitions Which Lead to Fluorescence and Phosphorescence. A = excitation to higher vibrational level of excited state, v_e in inset. C' = loss of excess vibrational energy. F = emission of energy back to ground electronic state, but at higher vibrational level, v_g in inset. T = transition from excited state to triplet state. P = slow emission of energy back to ground state by way of a "forbidden" transition.

v_g , now of the ground state. Again, thermal collisions remove the excess vibrational energy, C . The net result of this sequence is that the energy of the emitted light is less than that of the absorbed light; hence, the emitted light is of longer wavelength than that absorbed and may be visible even when the absorbed light is in the UV.

The transitions involved in fluorescence occur between *singlet states* (Fig. 33-12A), states in which all electrons are of antiparallel spins. Quantum selection rules predict that excitation simultaneous with spin reversal is improbable. There are also a number of *triplet states* (Fig. 33-12B), states in which two electrons are of parallel spins. The transition from the ground state to the lowest triplet state is often "forbidden," that is, very improbable. The molecule reaches this triplet state by transfer from the

MO's	ground singlet	1st excited singlet	2nd excited singlet	1st triplet	2nd triplet
3rd					
2nd					
lowest					
spin interactions with magnetic field:	only $\uparrow\downarrow = 0$ (single)			$\uparrow\uparrow = +1, \uparrow\downarrow = 0$ $\downarrow\downarrow = -1$ (triple)	

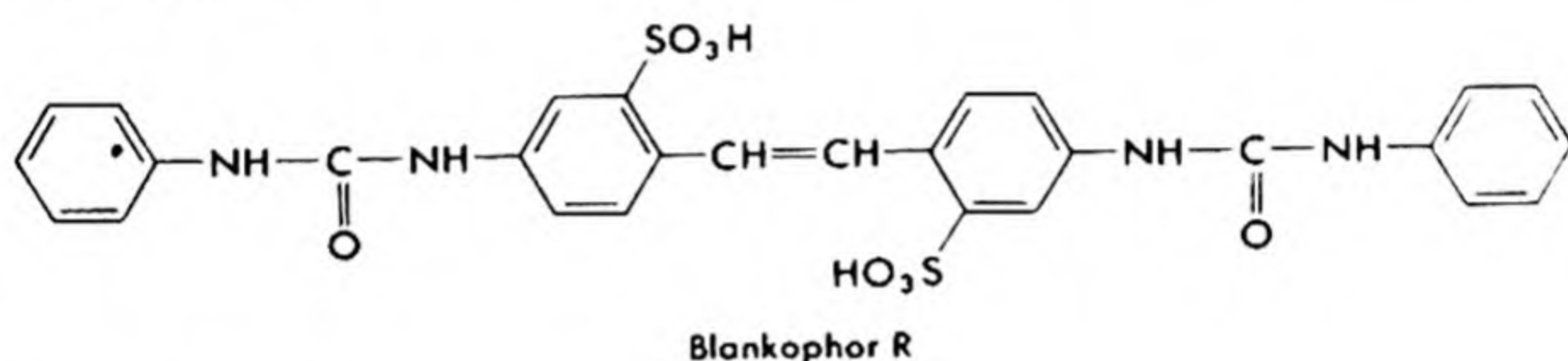
A

B

Fig. 33-12. Arrangement of Electrons in MO's in Singlet and Triplet States.

excited singlet state, T . Any energy evolved in this process may be lost through collisions. Now the molecule finds itself in a metastable energy state; to go directly to the ground state is an improbable transition, hence very slow. Thus, molecules emit the energy, P , over a long period of time, a phenomenon called *phosphorescence*. Fluorescence persists only about 10^{-8} sec. after the exciting energy source is shut off, that is, fluorescence occurs only during excitation. Phosphorescence, however, persists from 10^{-2} sec. up to several seconds after the exciting energy source is shut off.

A typical optical bleach, or "blankophor," is Blankophor R. It may be noted that this molecule does not have a long conjugated system (the longest is the central diaminostilbene system), hence does not absorb visible light. But it does have two diphenylurea systems and the central stilbene system, which can be expected to absorb intensely in the near UV. The emitted light, therefore, falls just into the visible region, in the blue end of the spectrum.



A. Direct Dyeing.

Application of a dye solution directly to a material to be dyed is called *substantive*, or *direct*, dyeing. The dyestuff must bond strongly to the fibers of the dyed material to be wash fast. Since salt-forming groups most successfully attract dye molecules, protein fibers such as wool and silk are most easily dyed by this method.

B. Mordant Dyeing

A trick used to make fibers with weak attraction for dye molecules, such as cellulose and its derivatives, take dyes effectively is to treat the fiber with an intermediate compound that bonds to the fiber and to the dye. This intermediary is called a *mordant*. Aluminum hydroxide and antimony compounds are mordants used with acid dyes. Tannic acid is used with basic dyes.

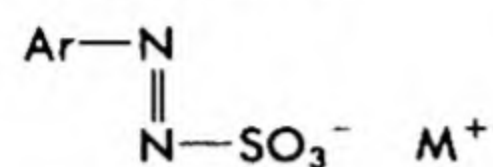
The fabric is treated with a solution of the metal salt or tannic acid, then dipped into a fixing solution to precipitate the mordant in the fiber. The prepared fabric is then dyed as in direct dyeing.

D. Developed Dyeing

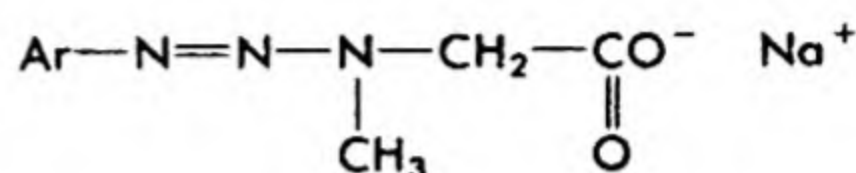
When an azo dye is coupled on the fiber surface, the process is called *developed* or *ingrain* dyeing. The dye is retained on the fiber mainly because of its insolubility. (See also azoic dyes, Table 33-4.)

The developing process is especially suitable for fabric printing. A paste containing the coupler and an inactive diazo precursor is printed on the fabric with rollers. Treatment of the diazo precursor with formic acid vapors, heat, or light forms the active diazonium salt, which immediately couples and forms the dye on the fabric. The paste matrix is then washed off.

Diazo precursors which are used are *antidiazosulfonates* and *diazo-amino compounds*.



arene-antidiazosulfonate
(heat or light activated)



arene-diazoamino compound
(acid activated)

D. Vat Dyeing

In vat dyeing a leuco base is dissolved in alkali or sodium sulfide solution. The fabric is soaked in the solution, then allowed to air-oxidize to the desired color intensity. A wash to remove the alkali or sulfide completes the process. (See indigoid dyes, Table 33-4.)

E. Diazotype Processes

Certain arene-diazonium fluoborates are stable enough to be isolated from solution and kept in the dark at temperatures up to 25°. Exposure of paper coated with such salts to UV light destroys the salts. When the paper also contains a coupling agent (phenol or arylamine) and is partly shadowed by a drawing or print, the shaded portion can be developed in ammonia fumes to give a direct positive print in any desired color (usually blue or black). The most widely applied variant is the Ozalid process, which has virtually displaced the old ferrous ferricyanide blueprint process in many applications.

33-4 INDICATORS

Indicators are colored organic compounds which change color reversibly with change of conditions in their solution. Two kinds of indicators are widely used in analytical work. One changes color with change in pH and is used for acidimetry. The other changes color with changes in oxidation potential of reagents in solution and is used for measurements of oxidizing and reducing agents.

Of the two, pH indicators are the more numerous and more common. They include several classes, among them basic triphenylmethanes, phthaleins, azo, and nitro compounds.

Unlike dyes, indicators can dispense with the virtue of affinity for fibers. However, intensity of color is necessary in at least one form of the indicator.

The principle utilized by pH indicators is a difference in mesomerism between the acid or base form of an indicator and its salts. These differences are shown for several indicators in eqs. (5) through (8), in which the more highly colored form is given to the left. The pH range of change of the indicator occurs from the pH at which the ratio of concentration of form A to form B is 1:10 to that at which the ratio of concentration of form A to form B is 10:1, approximately. This is a property of the sensitivity of the eye in discerning one color in the presence of the other. This range is one hundredfold or two pH units (see Fig. 33-13).

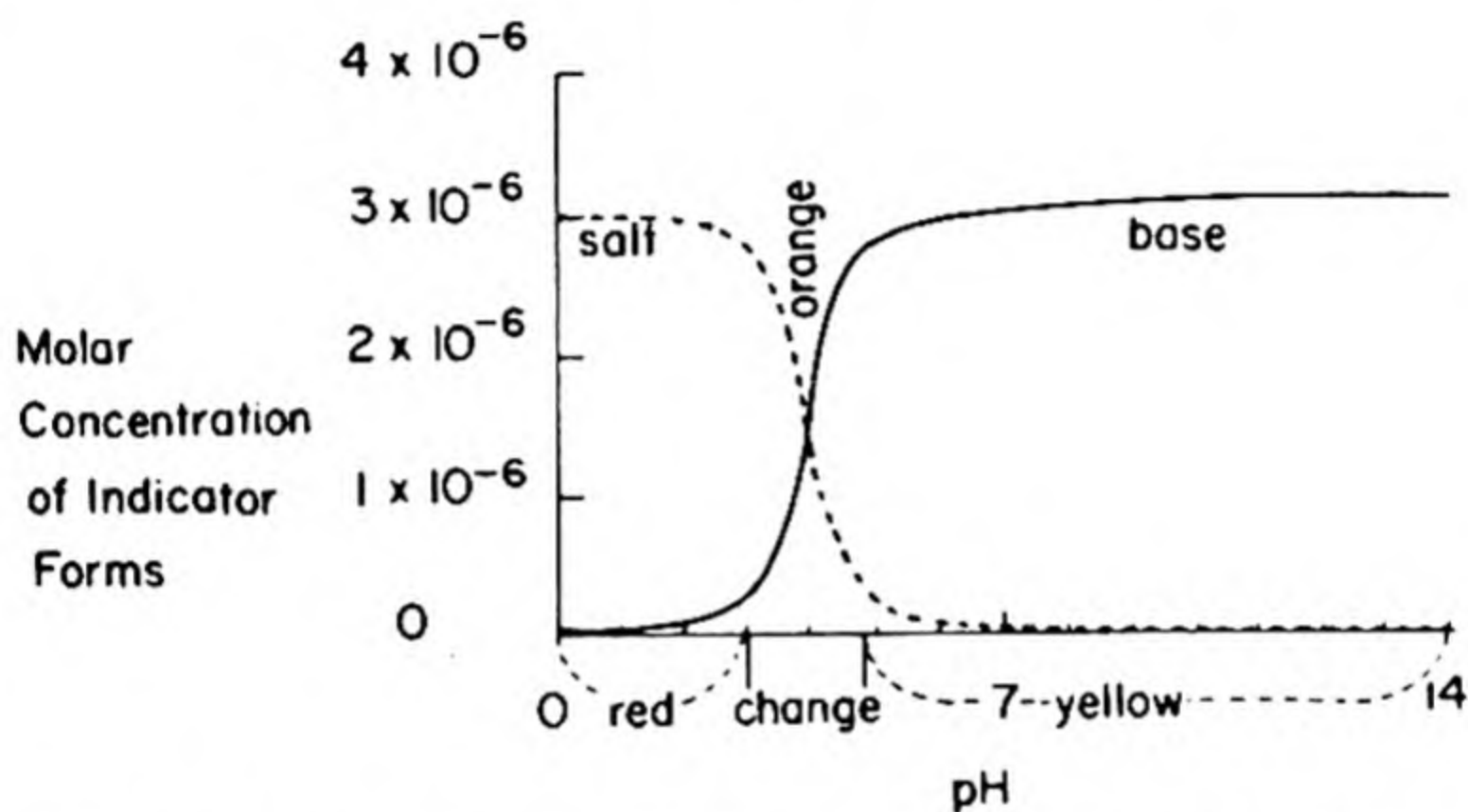
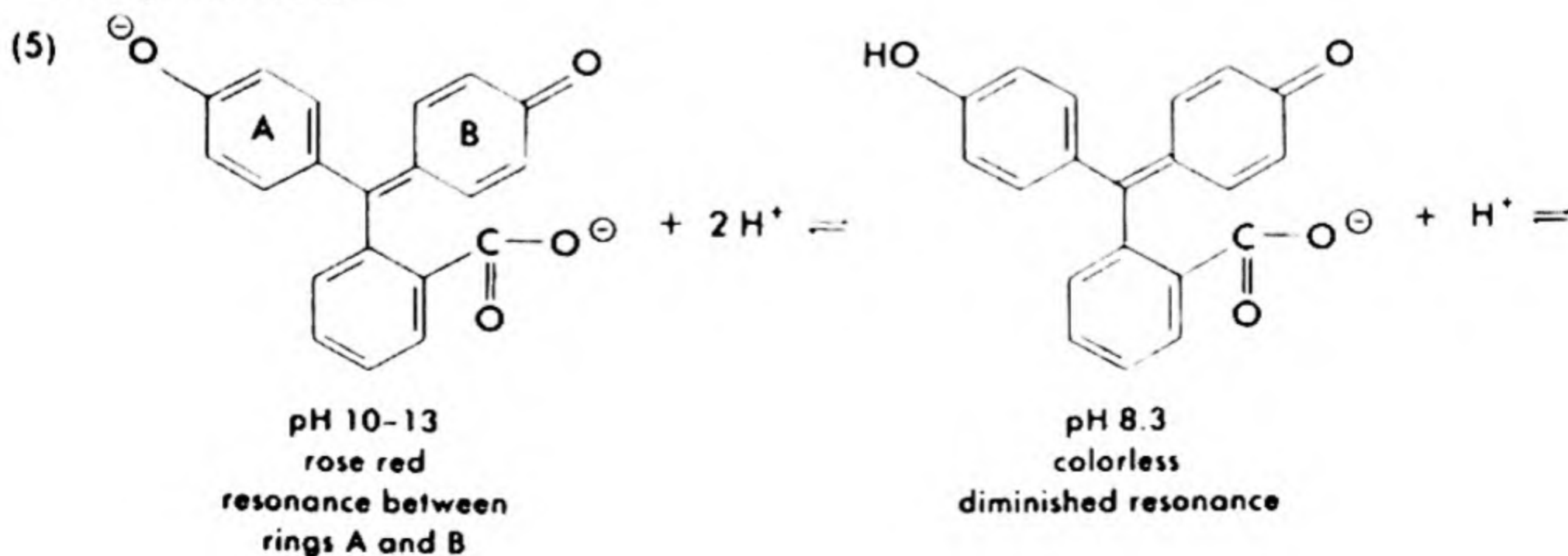
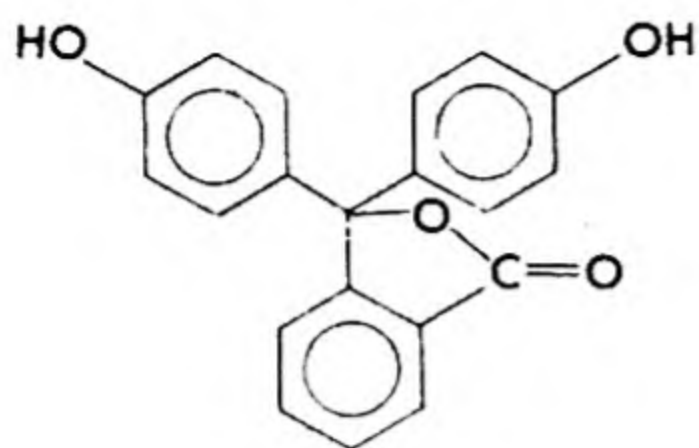


Fig. 33-13. Effect of pH on Concentration of Forms of Methyl Orange and Resultant Range of Color Change.

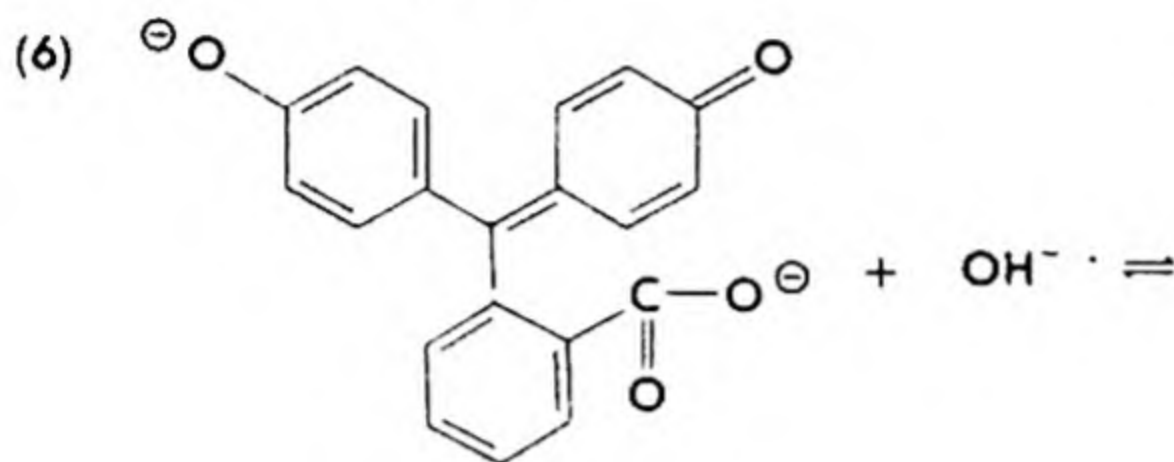
It is a difference in oxidation state that changes the resonance state of an oxidation-reduction indicator. Most dyes can be oxidized or reduced to forms of different colors, but few such changes are rapidly reversible. An example of a reversible redox indicator is methylene blue (eq. 9). Azine dyes in general are suitable redox indicators (see Table 33-4).

Phenolphthalein:

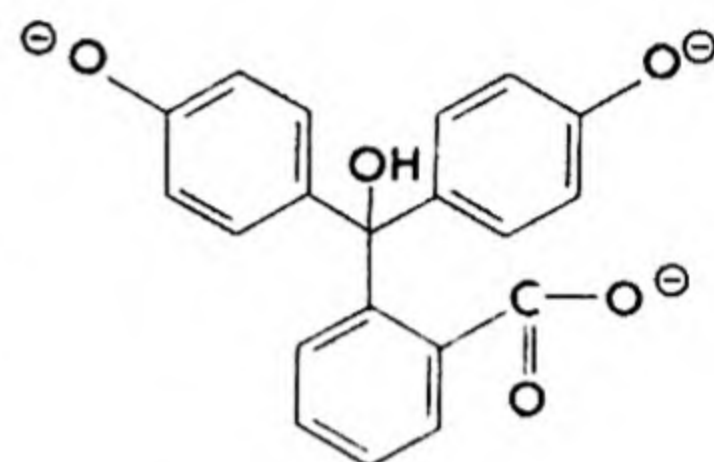




pH 0
colorless



pH 10-13

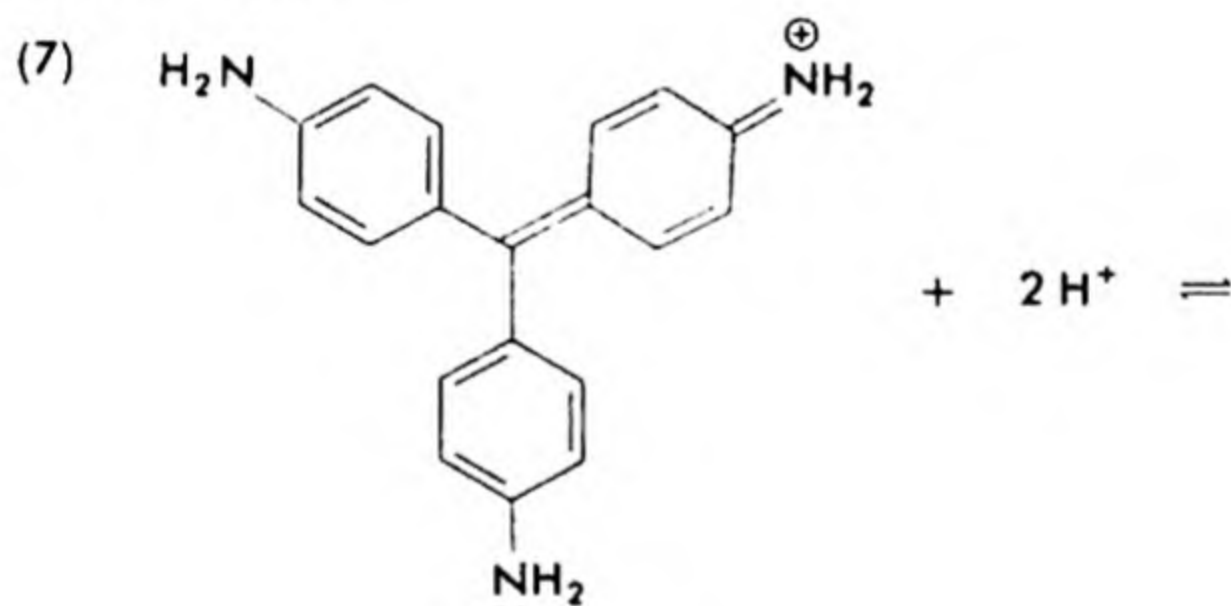


pH > 14

colorless

no resonance between rings

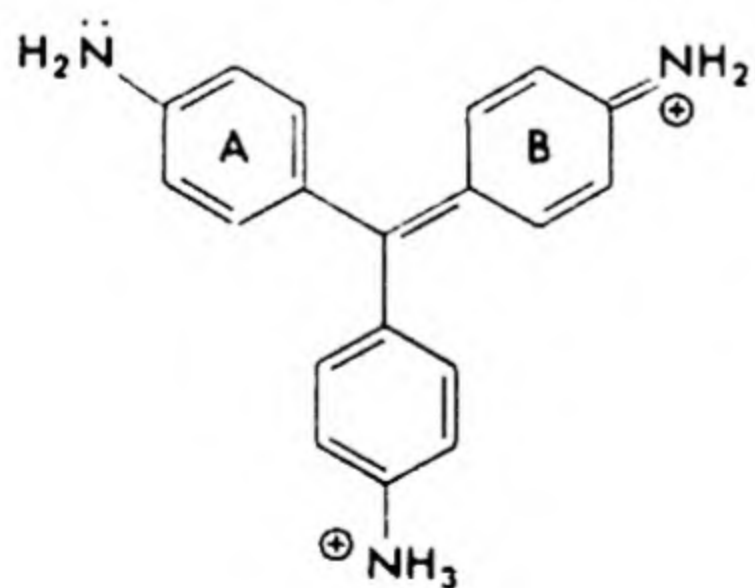
Methyl violet:



pH 3-14

violet

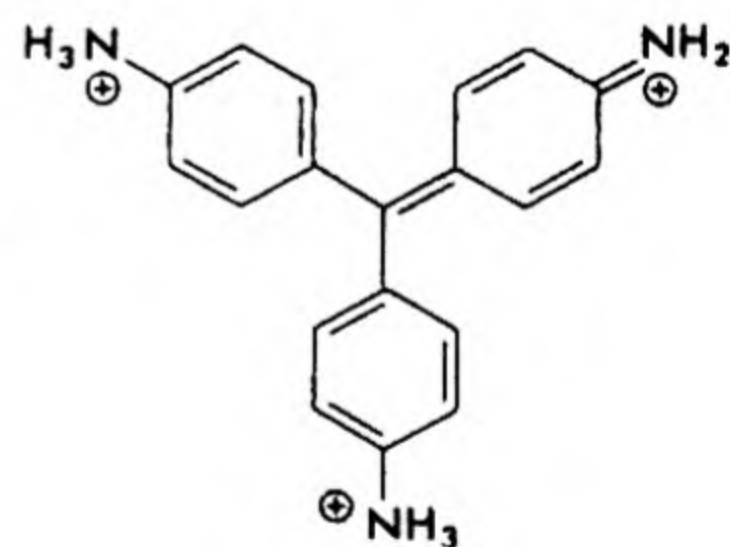
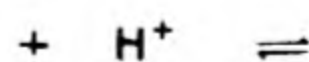
resonance among all three rings



pH 2

green

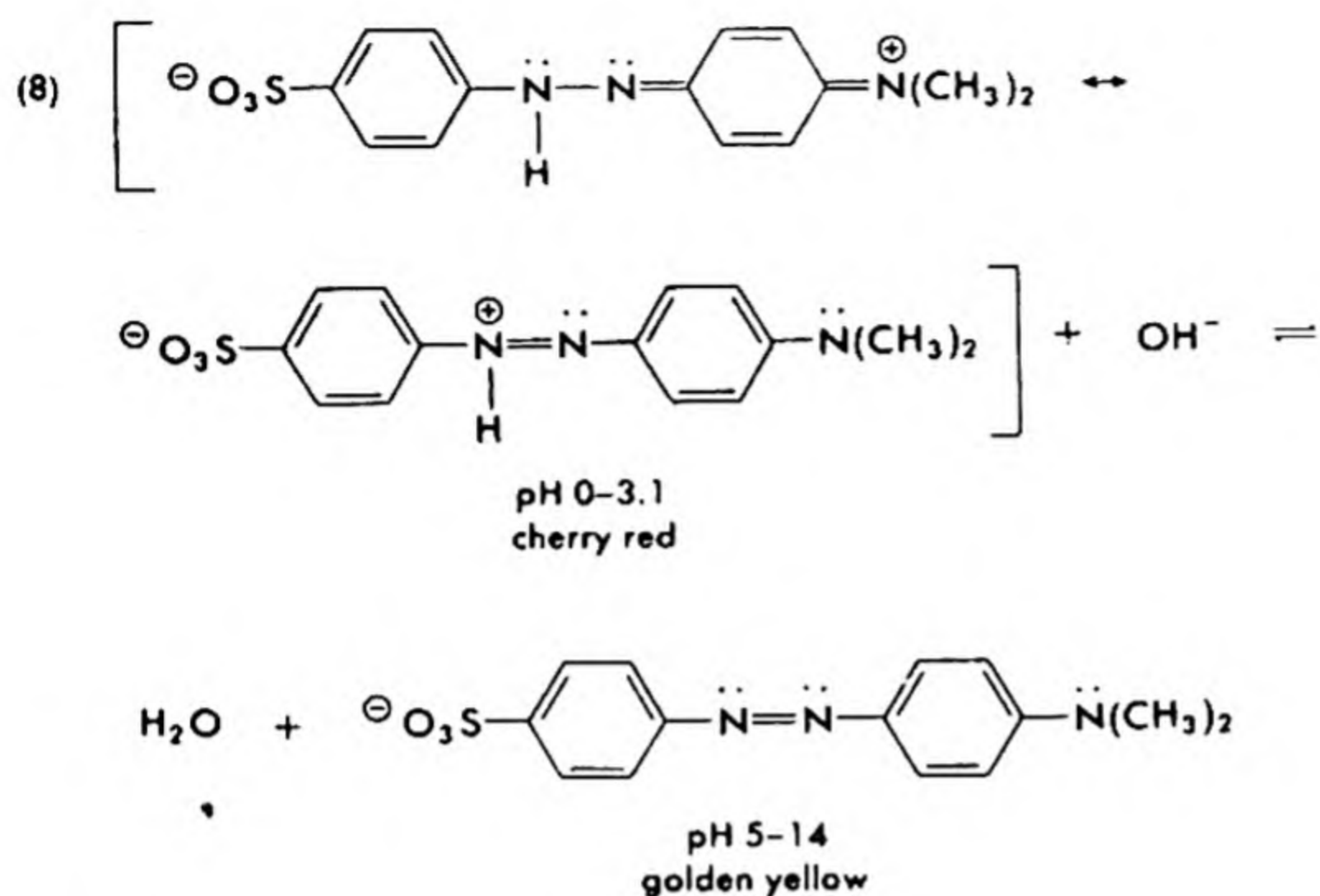
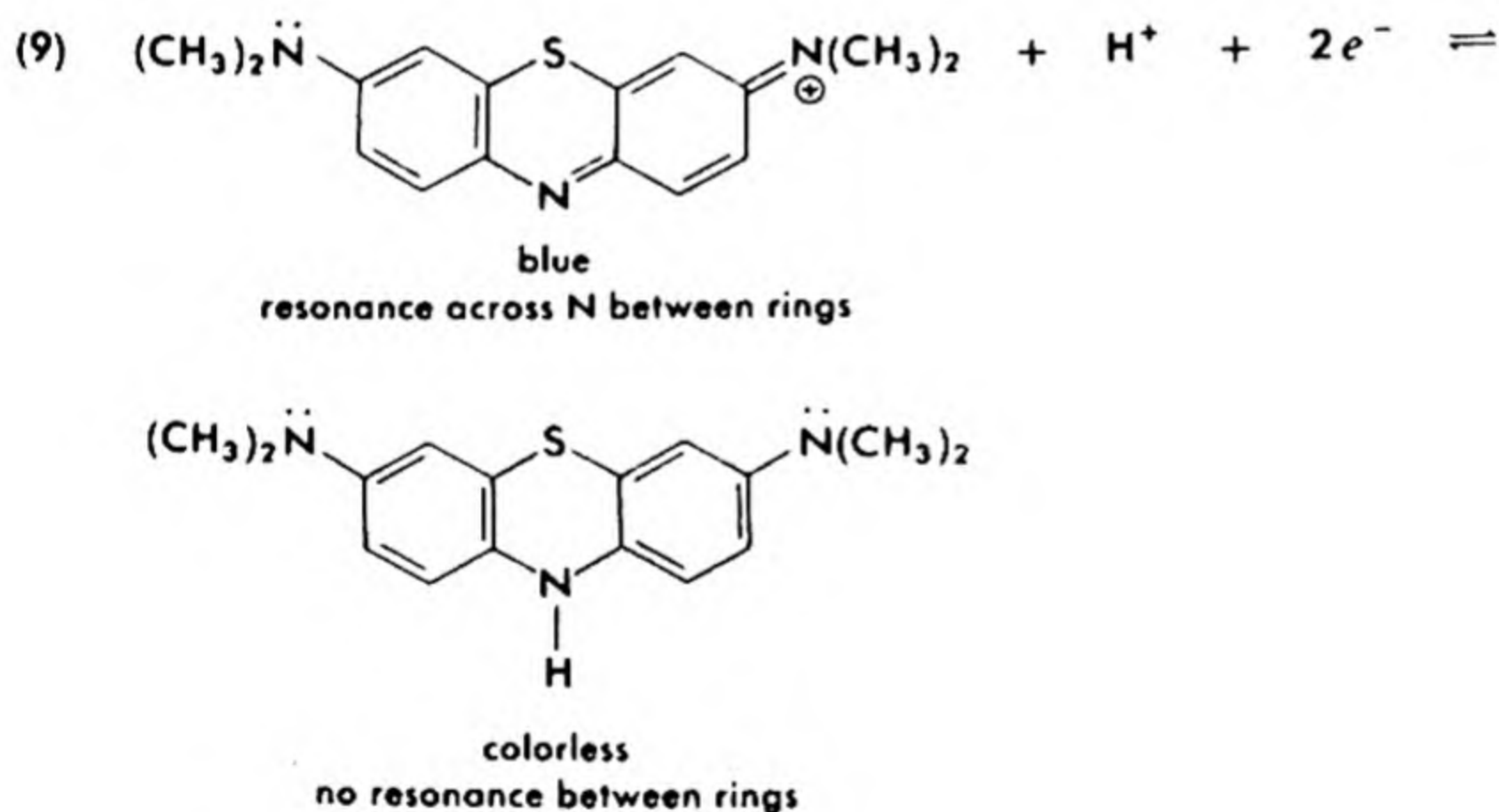
resonance between rings A and B



pH 0-1

yellow

diminished resonance

Methyl orange:*Methylene blue:*

SUPPLEMENTARY READINGS

- Bellamy, L. J., *The Infra-red Spectra of Complex Molecules*, 2nd Ed., Wiley, New York, 1958.
- Decelles, C., "The Story of Dyes and Dyeing" (a senior student paper), *J. Chem. Educ.* **26**, 593–587 (1949).
- Dyer, J. R., *Applications of Absorption Spectroscopy of Organic Compounds*, Prentice-Hall, Englewood Cliffs, N. J., 1965, Chapters 2 and 3.

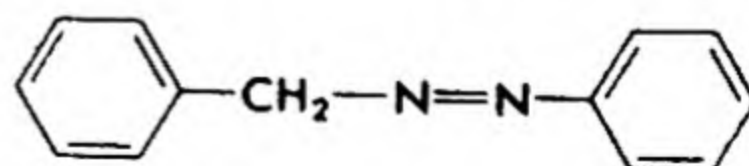
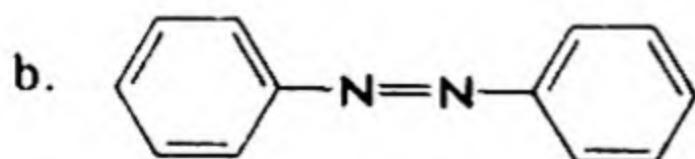
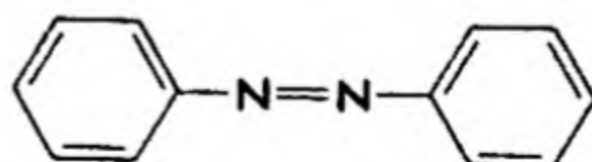
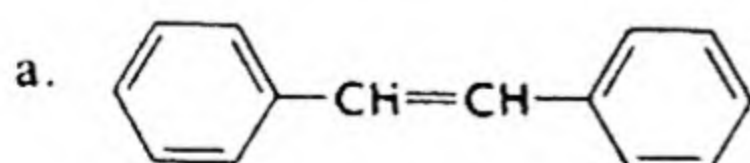
- Ferguson, L. N., *Electron Structures of Organic Molecules*, Prentice-Hall, Englewood Cliffs, N. J., 1952, Chapter 9, "Absorption Spectroscopy."
- Grimmel, H. W., "Organic Dyes," *Organic Chemistry III*, Wiley, New York, 1953, pp. 243-391.
- Jaffé, H. H., and M. Orchin, *Theory and Applications of Ultraviolet Spectroscopy*, Wiley, New York, 1962.
- Leermakers, J. A., and A. Weissberger, "Constitution and Physical Properties of Organic Compounds," *Organic Chemistry II*, Wiley, 1943, pp. 1778-1804.
- Nakanishi, K., *Infrared Absorption Spectroscopy-Practical*, Holden-Day, New York, 1962.
- Phillips, J. P., *Spectra-Structure Correlation*, Academic, New York, 1964.
- Robinson, R., "Sir William Henry Perkin: Pioneer of Chemical Industry," *J. Chem. Educ.* **34**, 54-58 (1957).
- Venkataraman, K., *The Chemistry of Synthetic Dyes*, Academic, New York, 1952.
- Wheeler, O. H., "Near Infrared Spectra of Organic Compounds," *Chem. Rev.* **59**, 629-666 (1959).

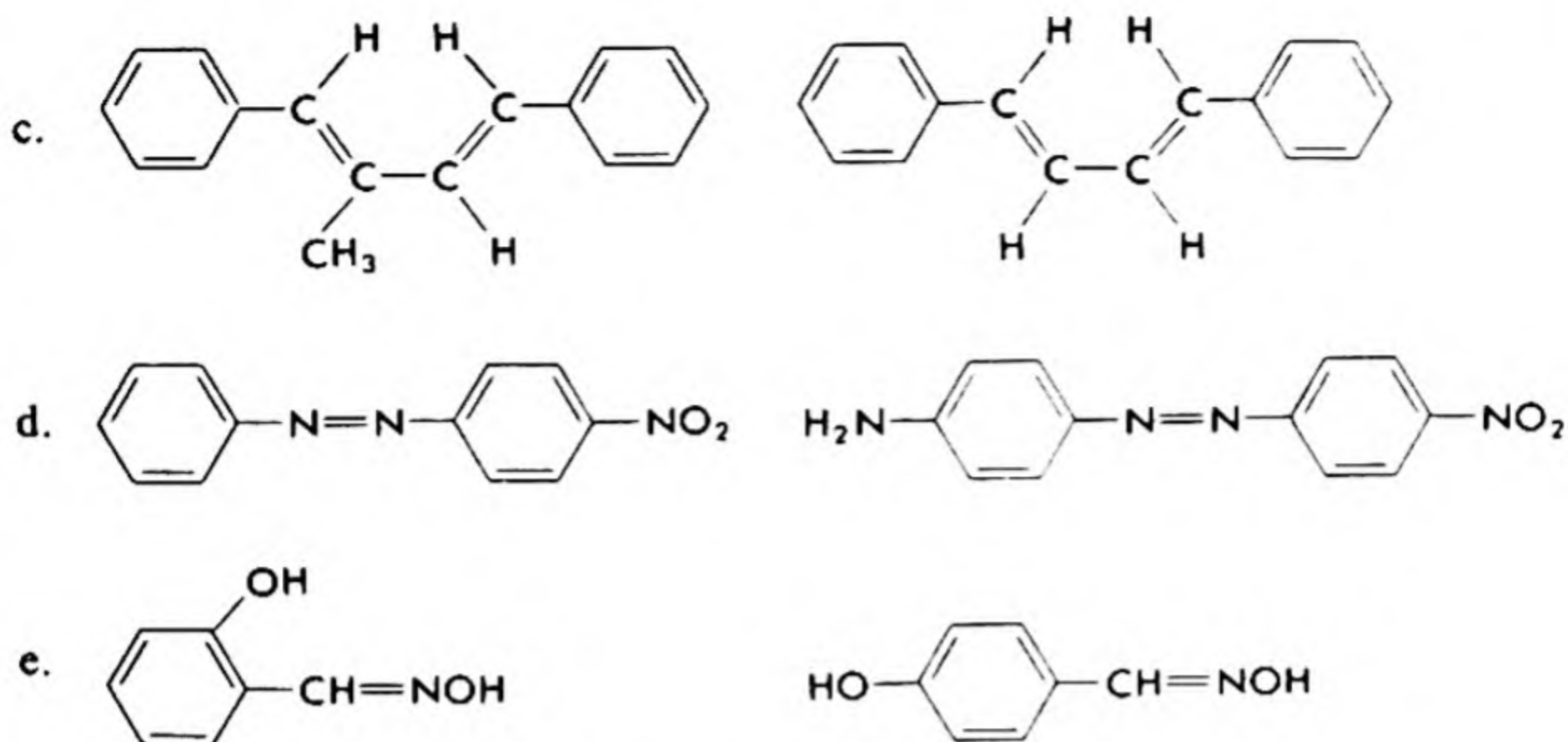
QUESTIONS AND PROBLEMS

1. Show by explanation, illustration, or definition that you understand what is meant by each of the following terms. Use diagrams wherever it is appropriate, but accompany them with verbal explanation.

- | | |
|------------------------|---------------------------|
| a. absorption spectrum | n. lake |
| b. auxochrome | o. mordant |
| c. azine dye | p. mordant dyeing |
| d. azo dye | q. nitro dye |
| e. bathochromic shift | r. optical bleach |
| f. chromophore | s. pigment |
| g. coupling agent | t. quinone dye |
| h. direct dyeing | u. rotational transition |
| i. dyestuff | v. sulfur dye |
| j. hypsochromic shift | w. triphenylmethane dye |
| k. indicator | x. ultraviolet region |
| l. infrared region | y. vat dye |
| m. ingrain dyeing | z. vibrational transition |

2. In each pair of compounds below, state which would be expected to absorb at longer wavelengths in the visible or ultraviolet range. Give the reasoning involved in your answer.





3. Compare infrared and ultraviolet absorption spectra in regard to:

- Type of information they give
- Sensitivity to solvents
- Ease of interpretation in terms of molecular structure.

4. Show how the following compounds can be prepared from benzene, toluene, naphthalene, anthracene, methanol, ethanol, acetic acid, and inorganic compounds, including phosgene. Indicate reagents and special conditions. Use structural formulas for organic compounds.

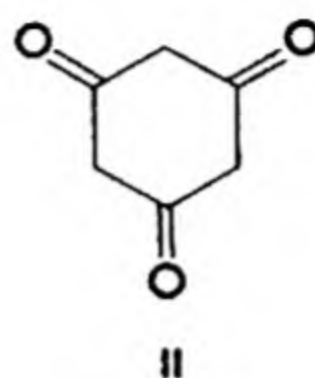
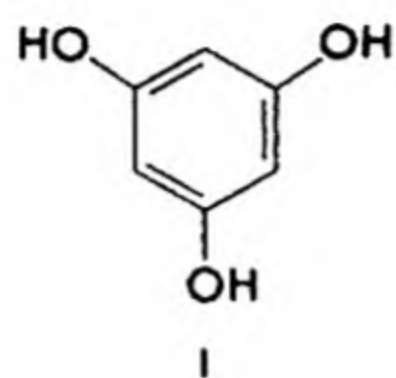
- 2-aminonaphthol-4,6-disulfonic acid
- primuline via *p*-toluidine
- benzidine-3,3'-dicarboxylic acid
- malachite green via benzaldehyde and dimethylaniline
- fluorescein
- chrome violet CG via salicylic acid and formaldehyde
- amido yellow E via 4-aminodiphenylamine-2-sulfonic acid
- helindon yellow CG via benzoquinone and *p*-chloroaniline
- capri blue via *p*-nitrosodimethylaniline and *p*-diethylaminocresol
- Blankophor R via 4-nitrotoluene-2-sulfonic acid and phenyl isocyanate
- ponceau red 2 R
- phenolphthalein
- methyl orange
- methylene blue
- fuchsin via *p*-toluidine and *o*-toluidine

5. Explain how an optical bleach, producing blue light by fluorescence, can make a yellowed material look white.

6. What structural features in a dyestuff provide for the formation of stable lakes and mordant dyes?

7. Write the equation for the pH equilibrium of alizarin yellow R. Which form should be more highly colored? (Note: this indicator has two regions of color change, one at pH 2-4, the other at pH 10-12. Can you write equilibria for both?)

8. Suggest a method by which the structure of phloroglucinol might be established to be either I or II.



34

Magnetic Resonance

34-1 SPIN PROPERTIES OF ATOMIC PARTICLES

A spinning charged body, such as an electron or an atomic nucleus, has a magnetic field (Fig. 34-1). In relation to an external field, the spin moment may be either parallel or opposed. The opposed moment has potential energy which tends to tip the spinning charge to its parallel position. Expressed in quantum terms, the spinning electron or a spinning spherical nucleus may have a quantum number of $+\frac{1}{2}$ or $-\frac{1}{2}$, depending on its orientation.

To tip the spinning charge so as to invert its spin direction absorbs or releases energy. The release of energy when an atomic particle changes spin is the basis of *magnetic resonance*.

In a uniform magnetic field the spinning particle cannot tip without some energy interaction. Instead it precesses, or wobbles (Fig. 34-2). The rate of precession depends on the magnetic field strength, μ_a .

In a rotating magnetic field, the spinning particle is acted upon unevenly by the field as it precesses. Little interaction results, however, until the frequency of oscillation exactly matches the frequency of precession. Under this condition, the spinning particle may be so disturbed as to tip over, with consequent release of energy. The oscillating field is said to be in magnetic resonance with the spinning particle when such an energy release is observed.

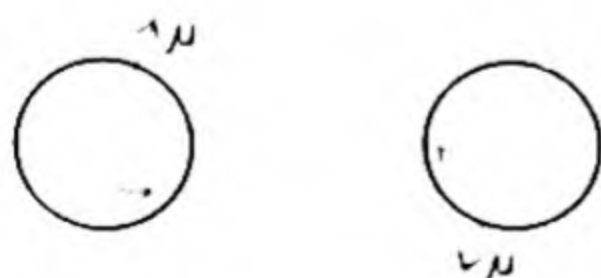


Fig. 34-1. Atomic Particles of Opposite Spin and Associated Magnetic Fields.

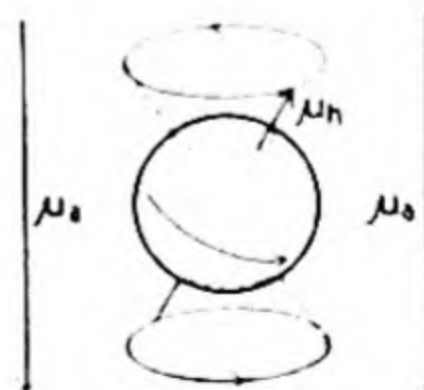


Fig. 34-2. Precession of Subatomic Particle. μ_h = magnetic field of particle, μ_a = applied magnetic field. The rate of precession depends on the magnetic field strength, μ_a .

When the applied magnetic field is removed, the nuclei or electrons oriented in preferred positions must lose their magnetic energy as thermal energy. This process is called *relaxation*.

34-2 APPARATUS FOR DETECTING AND MEASURING MAGNETIC RESONANCE

At least two types of magnetic resonance "spectrometers" have been devised, but their principle of operation is the same. The sample is suspended between the poles of a powerful electromagnet. A sweep circuit is placed at the ends of the pole pieces with its magnetic field parallel to that of the main energizing current. This provides a means of continuously varying the field strength.

At right angles to the sweep field is placed an oscillator coil, which provides the rotating magnetic field (see Fig. 34-3). The frequency of the

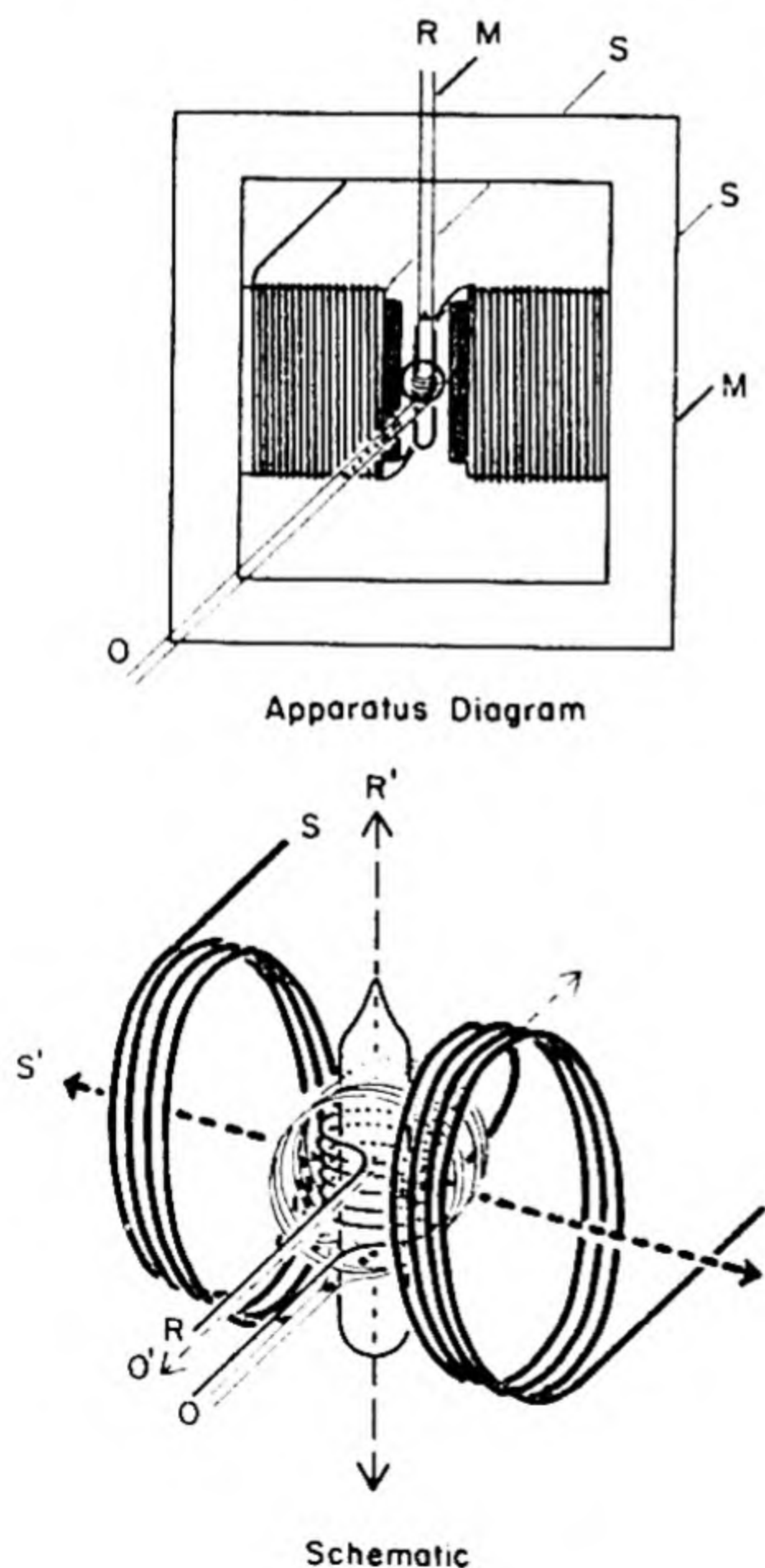


Fig. 34-3. Components of Magnetic Resonance Spectrometer. *M*, Main magnetic circuit. *O*, Oscillator circuit. *O'*, Oscillator field direction. *R*, Receiver circuit. *R'*, Receiver field direction. *S*, Sweep circuit. *S'*, Sweep field direction.

oscillator is fixed; the precession rate of the atomic particles is varied by varying the overall field strength.

A receiver coil is placed around the sample so as to detect magnetic oscillations occurring in the third axis, at right angles to the sweep field and the oscillating field. Specifically, the receiver detects the tipping over of atomic nuclei and electrons.

The usual magnetic field strength used for magnetic resonance (MR) measurements is 7,000–14,000 gauss.

34-3 NMR SPECTRA

The utility of nuclear magnetic resonance, NMR, lies in its ability to distinguish atoms of the same element on the basis of their environment. That is, like electromagnetic wave spectra, NMR spectra are structure-dependent. Naturally, atoms of different elements have different NMR properties; in fact, NMR is a powerful tool for distinguishing, indeed, for quantitatively analyzing for, isotopes.

The NMR properties of various atomic species are given in Table 34-1.

TABLE 34-1. Magnetic Properties of Atomic Nuclei^a

Nucleus	Mc./10,000 Gauss	% Natural Abundance	Relative Sensitivity ^b
^1_1H	42.6	99.98	1.000
^2_1H	6.5	0.016	0.0096
$^{13}_6\text{C}$	10.7	1.11	0.016
$^{14}_7\text{N}$	3.1	99.63	0.0010
$^{15}_7\text{N}$	-4.3	0.37	0.0010
$^{17}_8\text{O}$	-5.8	0.04	0.029
$^{19}_9\text{F}$	40.1	100.0	0.834

^a From Nuclear Magnetic Resonance by J. D. Roberts. Copyright 1959. McGraw-Hill Book Company. Used by permission.

^b For equal numbers of nuclei at constant field strength.

The column "Mc./10,000 gauss" shows the frequency-field strength relationship for each atomic species. Since the spectrometer can easily resolve differences of 5 milligauss/10,000 gauss, or the equivalent of frequency differences of 0.000005 Mc. (megacycles), the instrument can concentrate on one species of atom at a time.

For detecting different kinds of atoms, different fixed frequencies can be used. For the 60 Mc. frequency, ^1H is the range at $(60 \times 10,000)/42.6 = 14,000$ gauss. The separation of the atomic signals is directly propor-

tional to field strength; hence, there is a distinct advantage in operating at the maximum possible field strength.

The strength of the signal received, or detection sensitivity, is indicated in the last column. It is of interest that the hydrogen atom, ^1H , produces the most intense signal. This makes NMR a tool of choice for the determination of positions of hydrogen atoms.

The NMR spectrogram for ethanol at low resolution is given in Fig. 34-4. Three distinct signals are obtained. Since the amplitude of the signal is directly proportional to the number of nuclei present, the assignment of the three signals to the respective hydrogen atoms in the ethanol molecule is easy.

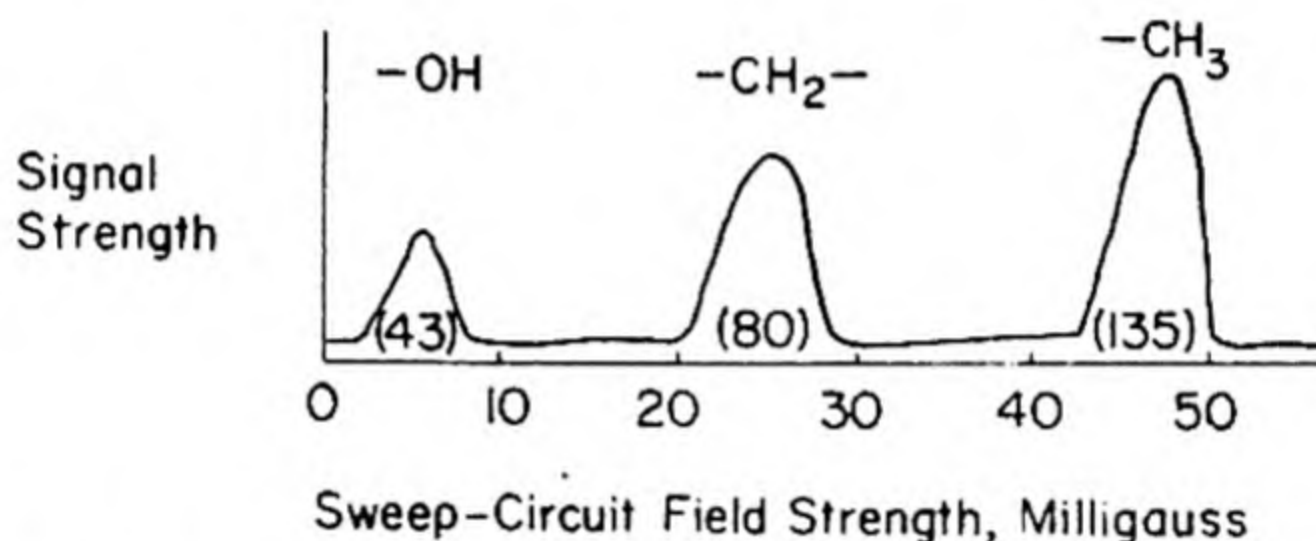


Fig. 34-4. Low-Resolution NMR Spectrogram of Ethanol at 9400 Gauss.

The question of why hydrogen atoms should give different peaks for different positions is answered in the interactions between the magnetic field and planetary electrons. The bonding and unshared electrons shield the nucleus; that is, they interact with the applied field so as to diminish it in the vicinity of the nucleus. Differences in bonding situations produce differences in the electronic environment. These differences are responsible for the so-called chemical shift illustrated in Fig. 34-4. (See the correlation table, Fig. 9-9.)

Higher resolution splits these simple peaks still further (Fig. 34-5). The finer peaks are produced by an effect different from that which gives the main peaks, as is indicated by the effect of different field strength. The distance between the main peaks ($H\delta$ in Fig. 34-5) is proportional to the field strength at which the measurement is made. The distances (J in Fig. 34-5) between the split peaks, however, are the same, regardless of field strength.

This finer splitting is called first order spin-spin splitting, since it results from the coupling of spins between different hydrogen atoms. Spin coupling between hydrogen atoms and carbon 12 atoms or oxygen 16 atoms is not involved except in the "chemical effect," since any atom with

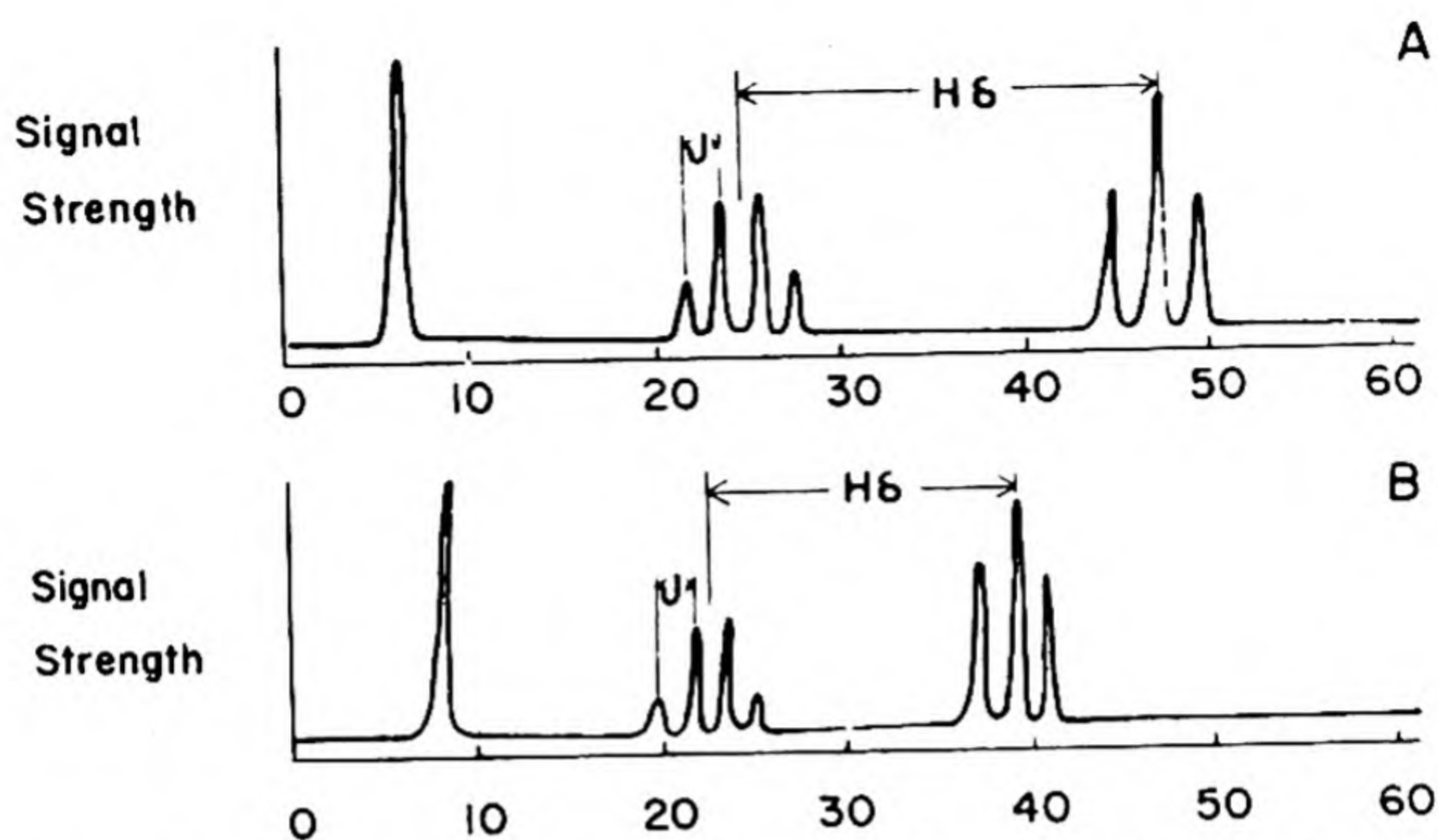


Fig. 34-5. High Resolution NMR Spectra of Ethanol. (A) Sweep Field Strength, Milligauss, at 9400 Gauss and 40 Mc, (B) Sweep Field Strength, Milligauss, at 7030 Gauss and 30 Mc.

an even number of protons and an even number of neutrons has a zero magnetic moment.

Spin coupling operates in this way. The possible totals of spin values in methyl and methylene hydrogen atoms are shown in Table 34-2. These values are important in their effects on the hydrogen atoms of the *adjacent groups*. Thus, the three possible total spin values of the methylene hydrogen atoms couple in three ways with the methyl hydrogen atoms. Coupling of +1 brings the peak a little sooner, -1 a little later, than 0, which has no effect. The proportion of these should be roughly 1:2:1, which is verified in the sizes of the methyl peaks. Coupling with ^{12}C and ^{16}O does not occur, since these atoms have spin moments of 0. However, spin coupling of protons with ^{13}C , ^{14}N , ^{30}P and other atoms to which the protons are attached can occur, since the number of protons or of neutrons or of each is odd.

The four total spin values of the methyl hydrogen atoms couple similarly with the methylene hydrogen atoms, resulting in four peaks with proportions of 1:3:3:1, in agreement with the number of combinations giving each type of coupling.

Failure of the methylene hydrogen atoms and the hydroxy hydrogen to interact is observed only when the alcohol is contaminated by a small amount of water or a trace of acid. Under these conditions, O—H bond forming and bond breaking occur faster than the oscillations by which the NMR measurement is made, and hydrogen on oxygen behaves independently of other hydrogen atoms in the molecule. When the alcohol is

pure and dry, splitting of the H—O peak by methylene and the reciprocal splitting of the methylene peak are observed (see Fig. 9-10).

Analysis of the curves from *n*-propyl alcohol, isopropyl alcohol, and *tert*-butyl alcohol (Fig. 34-6) serves further to illustrate the relationships between spectra and structure where fairly simple relationships are involved.

The alpha CH₂ group of 1-propanol is coupled with the three spin values of the beta CH₂ group (see Table 34-2). These couplings appear as the middle cluster of peaks (Fig. 34-6A).

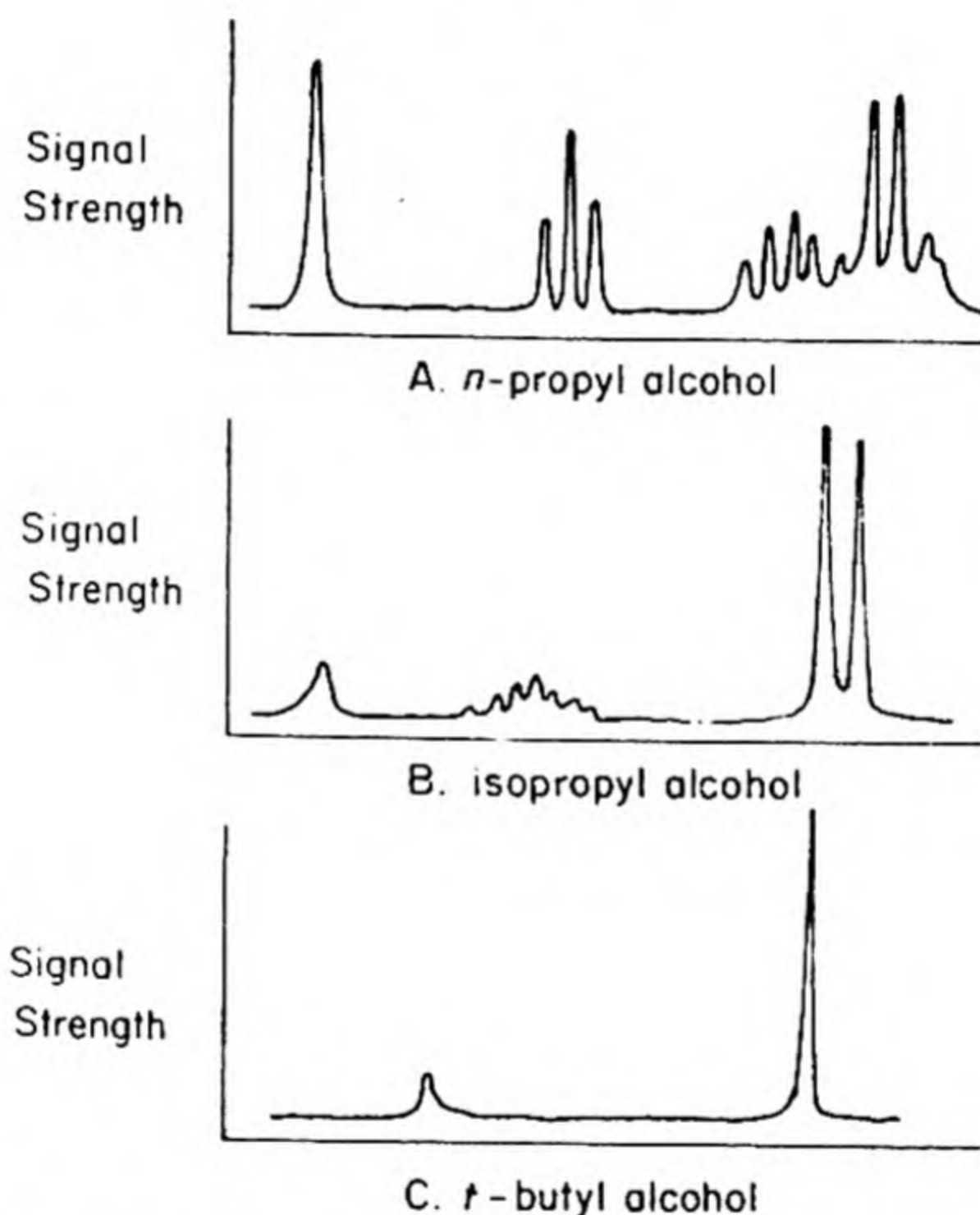


Fig. 34-6. Proton NMR Spectra of Alcohols at 9400 Gauss and 40 Mc.

The beta CH₂ group is coupled with the alpha CH₂ group and the three methyl hydrogens. These six peaks thus appear as a low cluster in the first half of the third series of peaks (Fig. 34-6A).

The methyl group is coupled with the beta methylene group to give three peaks, the first overlapping the sixth β -CH₂ peak. Some evidence for very weak coupling of the methyl hydrogens with the alpha methylene group appears in weak shoulders in the methyl triplet.

In isopropyl alcohol, the alpha hydrogen atom is coupled with two

TABLE 34-2

Coupling with Two Identical Hydrogens			Coupling with Three Identical Hydrogens		
Total	Graphic	Quantum Values	Total	Graphic	Quantum Values
+1	$\uparrow \uparrow$	$+\frac{1}{2}, +\frac{1}{2}$	$+1\frac{1}{2}$	$\uparrow \uparrow \uparrow$	$+\frac{1}{2}, +\frac{1}{2}, +\frac{1}{2}$
0	$\left\{ \begin{array}{l} \uparrow \downarrow \\ \downarrow \uparrow \end{array} \right.$	$+\frac{1}{2}, -\frac{1}{2}$ $-\frac{1}{2}, +\frac{1}{2}$	$+\frac{1}{2}$	$\left\{ \begin{array}{l} \uparrow \uparrow \downarrow \\ \uparrow \downarrow \uparrow \\ \downarrow \uparrow \uparrow \end{array} \right.$	$+\frac{1}{2}, +\frac{1}{2}, -\frac{1}{2}$ $+\frac{1}{2}, -\frac{1}{2}, +\frac{1}{2}$ $-\frac{1}{2}, +\frac{1}{2}, +\frac{1}{2}$
-1	$\downarrow \downarrow$	$-\frac{1}{2}, -\frac{1}{2}$	$-\frac{1}{2}$	$\left\{ \begin{array}{l} \uparrow \downarrow \downarrow \\ \downarrow \uparrow \downarrow \\ \downarrow \downarrow \uparrow \end{array} \right.$	$+\frac{1}{2}, -\frac{1}{2}, -\frac{1}{2}$ $-\frac{1}{2}, +\frac{1}{2}, -\frac{1}{2}$ $-\frac{1}{2}, -\frac{1}{2}, +\frac{1}{2}$
			$-1\frac{1}{2}$	$\downarrow \downarrow \downarrow$	$-\frac{1}{2}, -\frac{1}{2}, -\frac{1}{2}$

methyl groups to give seven peaks (Table 34-3). This hydrogen atom, in turn, has only two values, $+\frac{1}{2}$ and $-\frac{1}{2}$, to couple with the methyl hydrogen atoms, resulting in two strong peaks. The two methyl groups show no interaction at this resolution, since the hydrogen atoms are too far apart.

tert-Butyl alcohol has only two kinds of hydrogen, hydroxy and methyl, which do not interact when slightly moist. Hence, the two corresponding peaks are unique.

TABLE 34-3. Coupling Interactions with Two Methyl Groups

Total	Number of Couplings That Give Total
+3	1
+2	6
+1	15
0	20
-1	15
-2	6
-3	1

Even higher resolution shows finer second order spin-spin coupling interactions due to longer range interactions between hydrogen nuclei.

The foregoing discussion assumes that all of the bonds in the molecule are freely rotating. Coupling constants are extremely sensitive to the angular relationship between the protons concerned. Thus, eclipsed protons and *anti* protons on vicinal carbon atoms have large coupling constants, while there is little or no observable coupling when the dihedral

angle (§5-1B) is around 90° . Such data have been used for structural analysis in cyclic systems. See Fig. 34-7 for the relationship between the coupling constant, J (see §34-3 and Fig. 34-5), and the dihedral angle.

When, in very complex molecules, there is doubt concerning the assignment of PMR peaks to specific hydrogen atoms, one or more hydrogens may be replaced by deuterium atoms, which then fail to give peaks and which interact differently with adjacent hydrogens. The differences between the spectra for ordinary and deuterated molecules thus identify the hydrogens responsible for certain peaks.

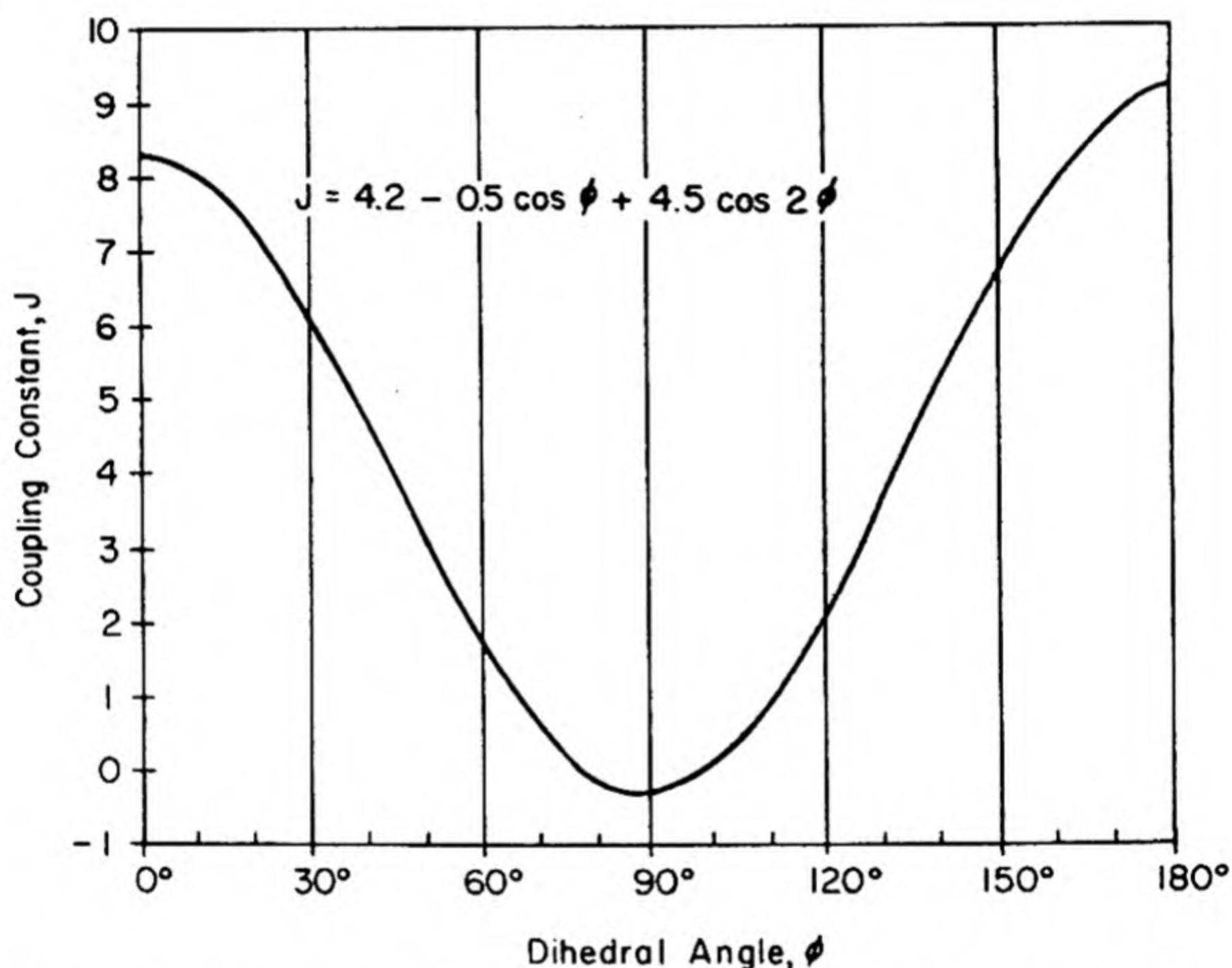


Fig. 34-7. Variation of Coupling Constant, J , with Dihedral Angle for Vicinal Hydrogen Atoms on Saturated Carbon Atoms. Equation of M. Karplus, *J. Am. Chem. Soc.* **85**, 2870 (1963).

34-4 ELECTRON PARAMAGNETIC RESONANCE SPECTRA

Electron paramagnetic resonance, EPR, also called electron spin resonance, ESR, differs in two respects from NMR. First, the resonant frequency of electrons for a given field strength is much higher than for atomic nuclei. This requires some modification of the apparatus for application to EPR work. Second, electrons are much more highly restrained in their response to spin tipping than atomic nuclei.

The restrictions on electrons result from the exclusion principle. When

electrons are paired to give stable orbitals, the lower orbitals are completely filled, with two electrons of opposite spin in each. An electron cannot be tipped over, therefore, without raising it to an excited state, which requires considerably more energy than the magnetic resonance technique provides.

Consequently, only unpaired electrons respond to magnetic resonance. This makes any free radical as obvious to magnetic resonance as a mountain in the middle of a plain. The main use of EPR, therefore, has been to detect the presence of free radicals during chemical reactions and to determine structures of radical species.

SUPPLEMENTARY READINGS

- Bhacca, N. S., and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry. Illustrations from the Steroid Field*, Holden-Day, New York, 1964.
- Brownstein, S., "High-Resolution Nuclear Magnetic Resonance and Molecular Structure," *Chem. Rev.* **59**, 463-496 (1959).
- Corio, P. L., "The Analysis of Nuclear Magnetic Resonance Spectra," *Chem. Rev.* **60**, 363-429 (1960).
- Dyer, J. R., "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, Chapter 5.
- Jackman, L. M., *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon, London, 1959.
- Pake, G. E., "Magnetic Resonance," *Sci. Am.* **199**, 58-66 (August, 1958).
- Roberts, J. D., *Nuclear Magnetic Resonance*, McGraw-Hill, New York, 1959.
- Roberts, J. D., "Nuclear Magnetic Resonance Spectroscopy," *J. Chem. Educ.* **37**, 581-584 (1961).

QUESTIONS AND PROBLEMS

1. Show by explanation, illustration, or definition that you understand what is meant by each of the following terms. Use diagrams where it is appropriate, but accompany them with verbal explanation.

- | | |
|-------------------|------------------------|
| a. chemical shift | d. nuclear relaxation |
| b. EPR | e. spin-spin splitting |
| c. NMR | f. sweep field |

2. What distinct advantage does NMR have over other physical methods for determination of structure?

3. How is EPR limited in its application to organic compounds?

4. What is the peculiar strength of EPR as a tool for the study of organic chemistry?

5. Predict the high-resolution sweep curves of the following compounds at 14,000 gauss and 60 Mc. Draw the predicted curves.

- | | |
|----------------------|------------|
| a. methanol | c. ethane |
| b. neopentyl alcohol | d. propane |



Electric Dipole Moments

35-1 BEHAVIOR OF POLAR MOLECULES

A polar molecule placed in an electrical field tends to orient itself parallel to the field, as in Fig. 35-1B. Charges of the polar molecules near the plates tend to neutralize the charges of the plates, thus increasing the capacitance of the plates.

The dielectric constant, ϵ , of a substance is thus measured by the effects of the substance on the electrical properties of a capacitor. Suitable calculations derive from this a *dipole moment* for the substance.

The dipole moment, μ , is the twisting force (torque) exerted on a molecule in the position shown in Fig. 35-1A, when the electric field strength is unity. In reference to the molecule, the dipole moment is described by eq. (1)

$$(1) \quad \mu = dq^+ + dq^- = 2dq^\pm = lq^\pm$$

where q^+ is the magnitude of the charge of the positive pole; q^- , the magnitude of the charge of the negative pole; d , the distance from the center of charge density (c in Fig. 35-1) to either pole, and l the distance between the charges.

The dipole moment can be expressed in electrostatic unit-centimeters, or in the more convenient Debye unit, 10^{-18} e.s.u.-cm.

35-2 RELATIONSHIP OF DIPOLE MOMENT TO STRUCTURE

The dipole moment of a molecule is the result of unequal sharing of valence electrons between atoms and the orientation of atoms in the molecule. Dipole moments are thus closely related to structure.

A. Molecular Moments as Vector Sums

The directional qualities of atomic bonding characteristics are clearly illustrated in the dipole moments of benzene derivatives. Vector addition principles are adhered to rather well if the polar groups are not conjugated with each other. The principles of vector addition are illustrated in Fig. 35-2 and eqs. (2) through (5) (law of cosines).

- (2) $\mu_p = \mu_1 - \mu_2$
 (3) $\mu_m = (\mu_3^2 + \mu_4^2 - \mu_3\mu_4)^{1/2}$
 (4) $\mu_o = (\mu_5^2 + \mu_6^2 + \mu_5\mu_6)^{1/2}$

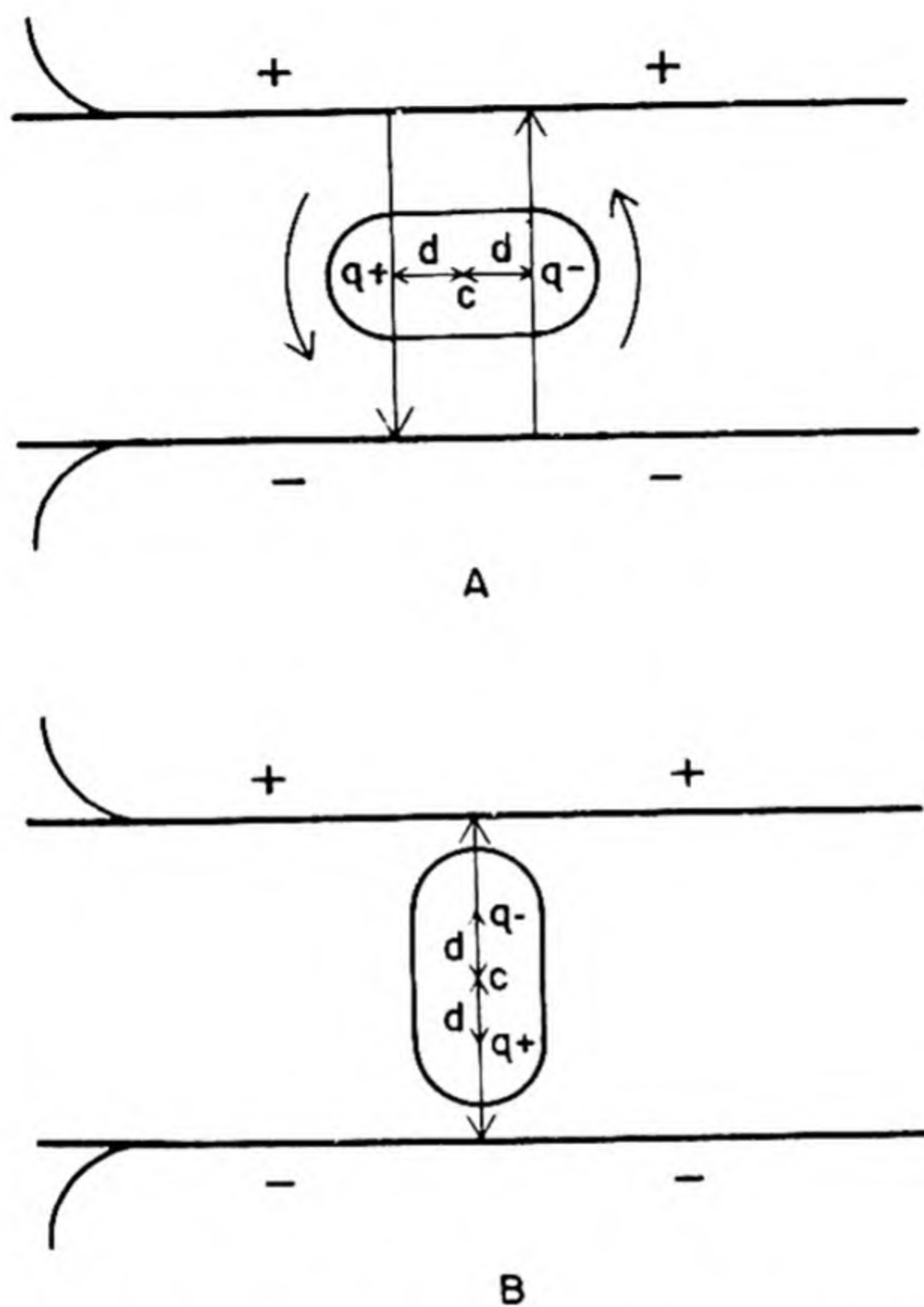


Fig. 35-1. Action of Electric Field on Molecular Dipole. (A) Oriented perpendicular to field, (B) Oriented parallel to field.

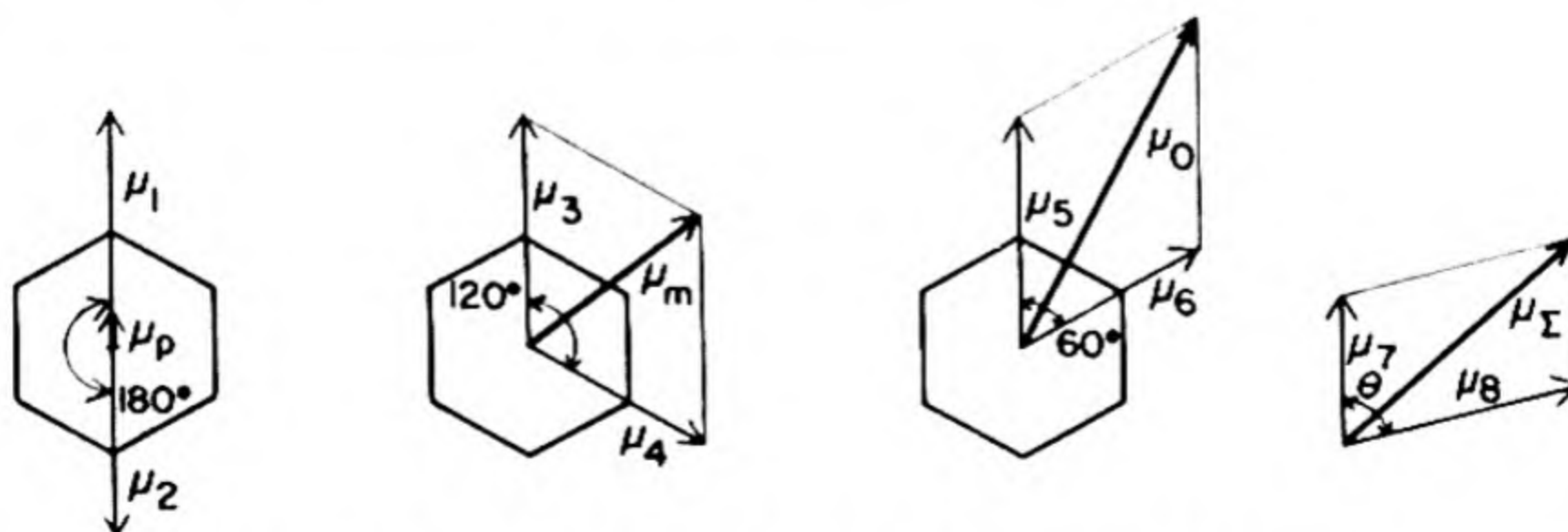


Fig. 35-2. Calculation of Dipole Moment Vectors.

In general:

$$(5) \quad \mu_{\Sigma} = (\mu_7^2 + \mu_8^2 + 2\mu_7\mu_8 \cos \theta)^{1/2}$$

The simple additive quality of dipole group moments acting in the same direction is shown in Fig. 35-3. This applies only when the two groups do not reinforce each other by resonance. Mesomeric interaction augments the total dipole moment (Fig. 35-4).

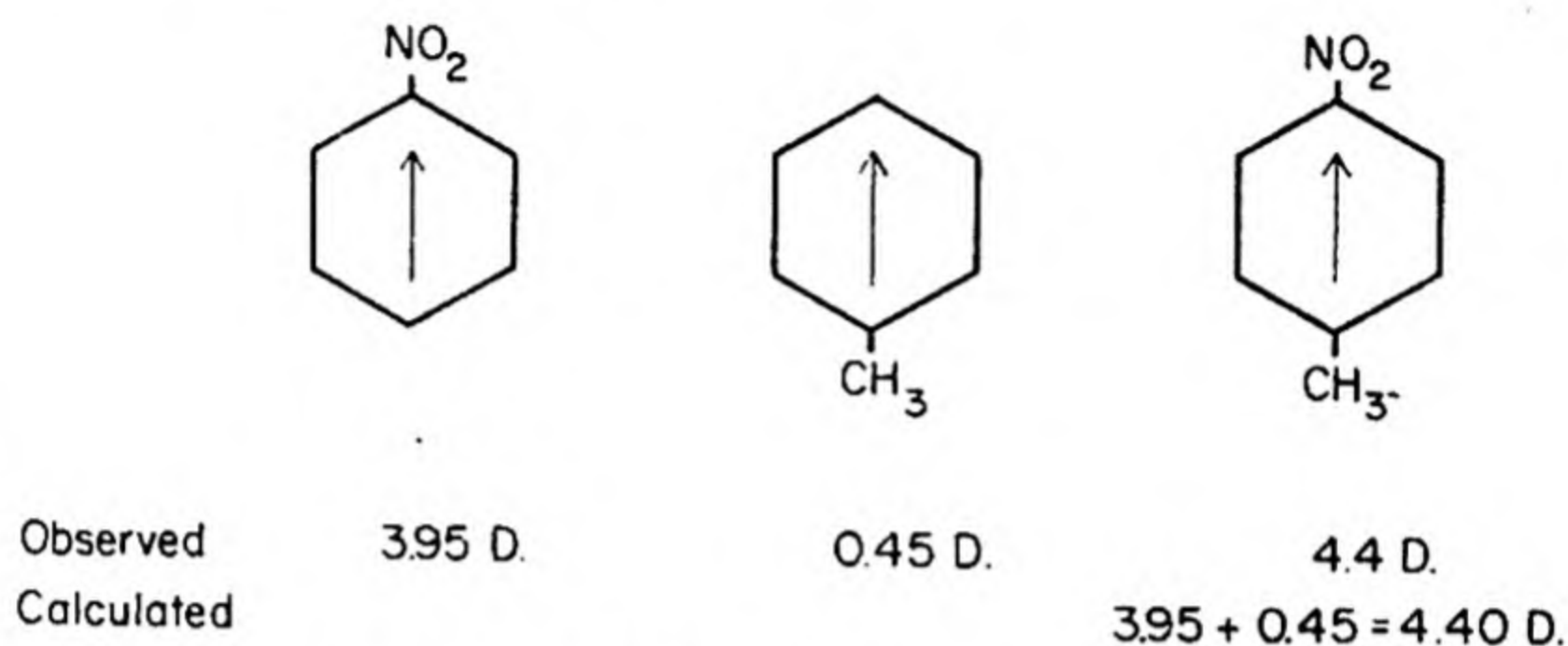


Fig. 35-3. Additivity of Group Moments.

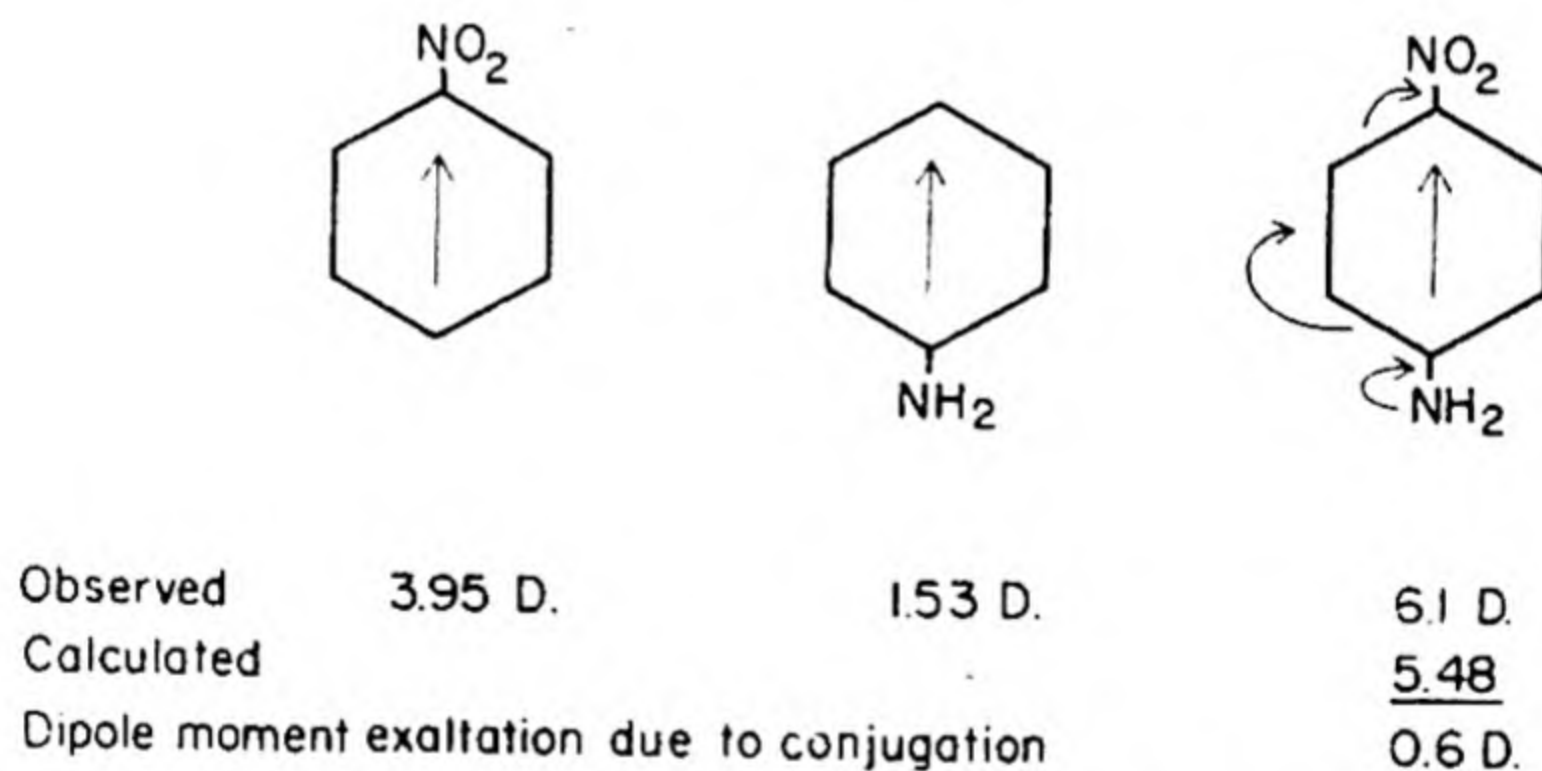


Fig. 35-4. Effect of Increased Resonance on Group Moment Additivity.

Vector additivity of group moments, when these are not in line, is illustrated in Fig. 35-5. Groups *ortho* to each other interact in two ways to diminish the observed dipole moment. Groups with like charges, or bulky groups, repel each other enough to widen the angle appreciably. In addition, similar groups on adjacent carbon atoms each pull against a charge induced by the other group, so that both group moments are decreased. Where the group moments are in the opposite direction, as in *o*-chlorotoluene, there seems to be little interaction.

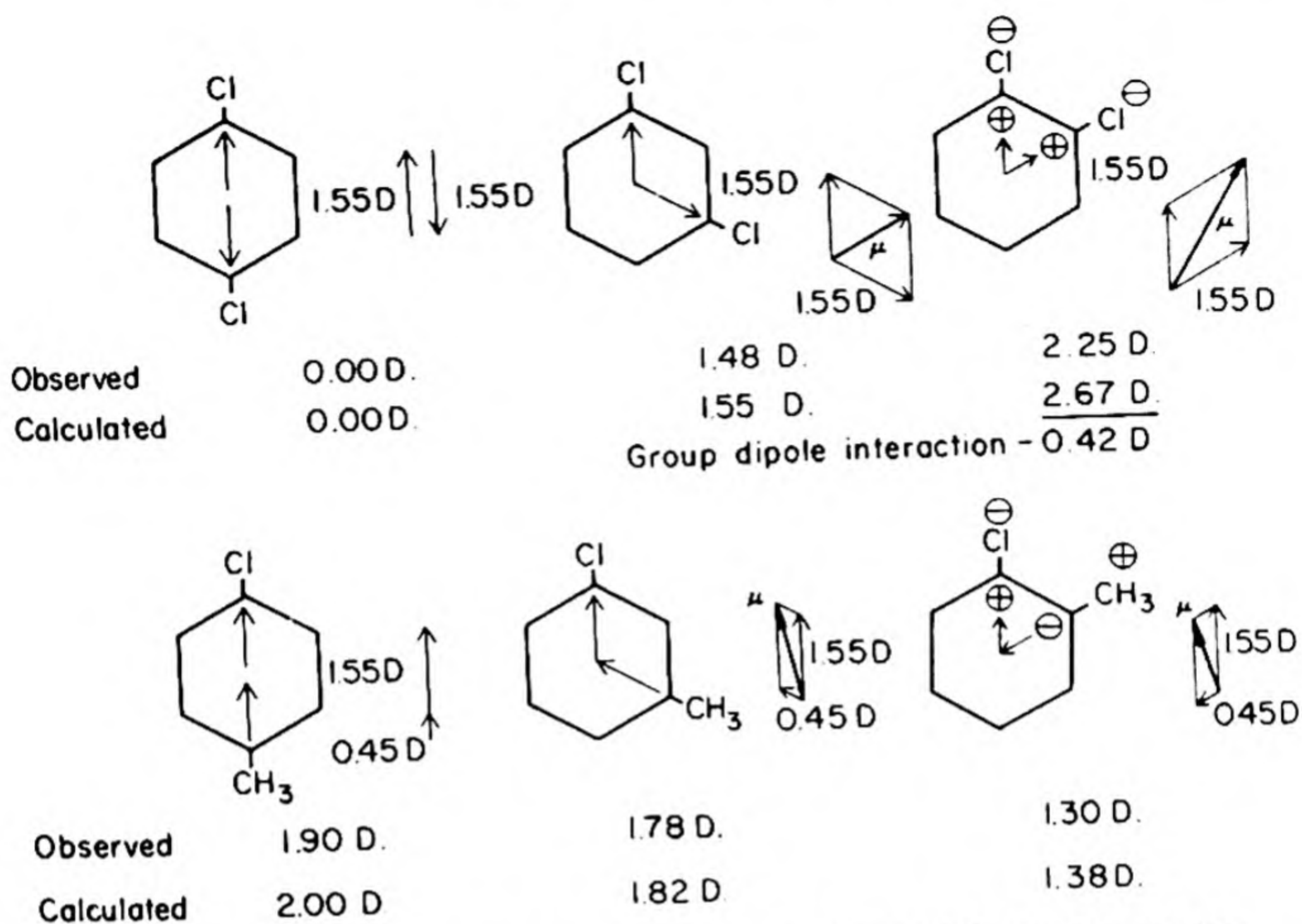


Fig. 35-5. Vector Addition of Group Moments. Case of Group Interaction.

Addition of group moments in aliphatic compounds is somewhat more complicated because the moments do not lie in the same plane, but can be handled by three-dimensional trigonometry.

Poor agreement between calculated and observed values is obtained because of group interaction when the polar groups are on the same carbon atom (Fig. 35-6).

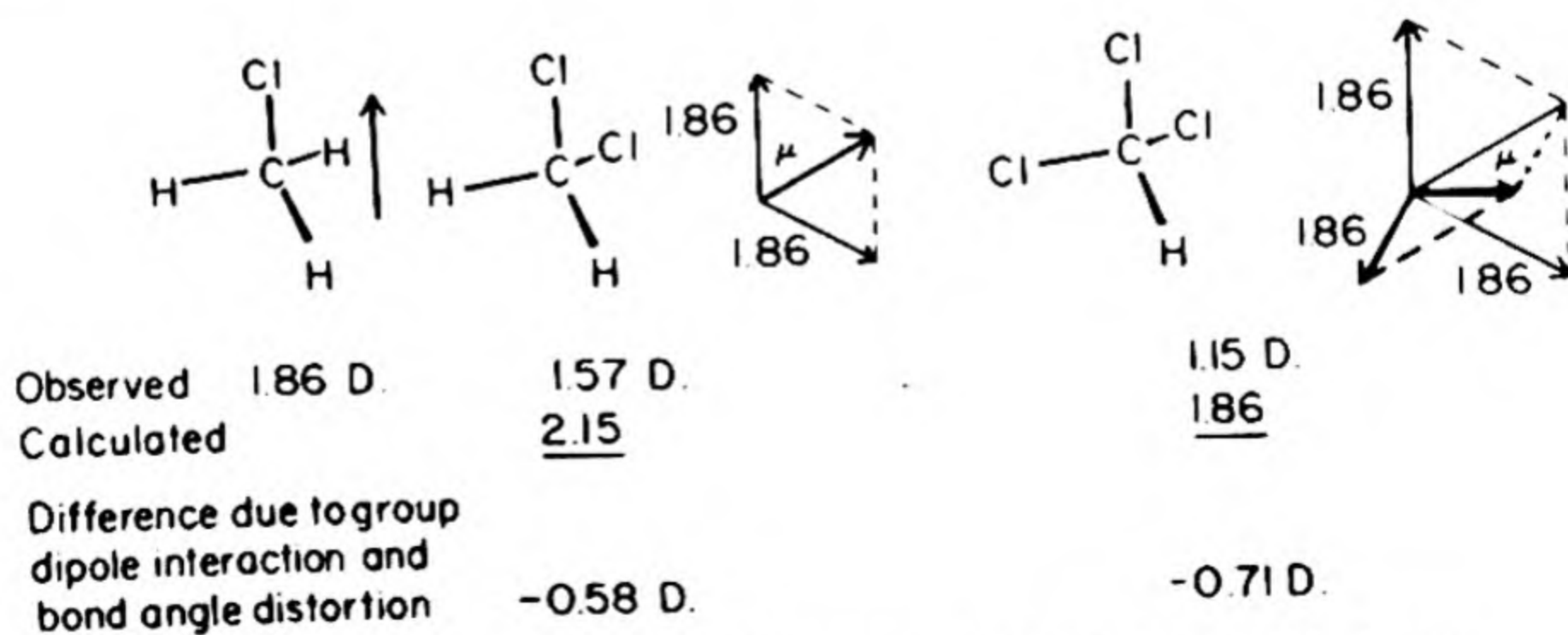


Fig. 35-6. Vector Addition of Moments in Chlorinated Methanes.

B. Using Dipole Moments to Determine Structure, Configuration, or Conformation

For many simple cases of the nature of those heretofore described, comparison of observed dipole moments with moments calculated from known group moments, taking into account *ortho* effects and effects of cumulative substitution of a carbon atom, can provide the key necessary to establish a structure.

Another situation in which dipole moments are quite helpful is the elucidation of *cis* and *trans* configurations. Valid interpretation requires determination of the direction of the dipole with respect to the double bond, whether parallel, or transverse, as well as whether group moments lie along carbon-group bond directions. *trans*-Isomers in which the groups B and C (Fig. 35-7) are identical and the groups A and D are identical are nonpolar, provided the directions of group moments lie along the carbon-group bonds, while the *cis*-isomers are polar.

$$(7) \quad \mu_{trans} = \mu_B - \mu_C$$

$$(8) \quad \mu_{cis} = [(\mu_A - \mu_B)^2 + (\mu_A - \mu_C)^2 + 2(\mu_A - \mu_B)(\mu_A - \mu_C) \cos 60^\circ]^{1/2}$$

When, due to freedom of rotation, groups can take positions which differ in resultant dipole moments, calculation of the average moment involves integration of complex trigonometric functions.

In all of the calculations given, the group moments have been taken as if carbon-hydrogen bond moments do not count. Actually, the carbon-hydrogen bond must have a group moment. However, because of the tetrahedral or hexagonal symmetry of compounds of carbon, it is impossible to compute directly the pure bond moments for every group in the molecule, including hydrogen atoms. Carbon-hydrogen bond moments

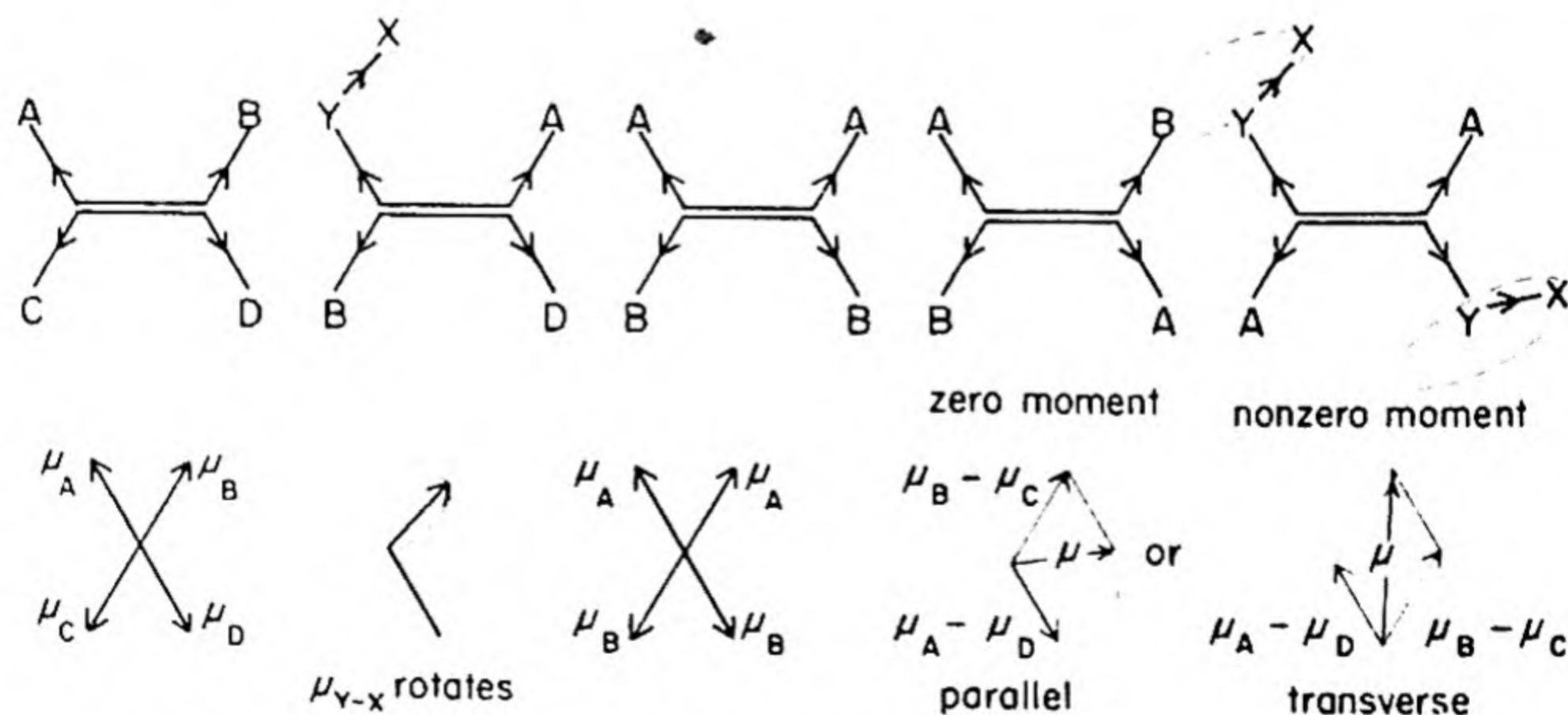


Fig. 35-7. Determination of *Cis-trans* Isomers by Dipole Moments.

can be estimated, however, from similar moments on unsymmetrical atoms such as oxygen and nitrogen, together with the electronegativity values for the several atoms.

Group moments might be expected to remain the same in all situations not involving changes in resonance or other group interaction. This is only approximately true. The inductive effect in long chains tends to lengthen the distance between charge centers and thus to increase dipole moments. However, to the accuracy with which these values are now obtainable, the inductive effect is not appreciable beyond the second carbon atom.

TABLE 35-1. Average Group Moments for Aromatic Substituent Groups in Vapor (v) and Solution (s)

Group	Moment (D.)	Group	Moment (D.)
CH ₃	+0.37 (v)	—NC	—3.49 (s)
	+0.45 (s)	F	—1.57 (v)
—CN	—4.37 (v)		—1.43 (s)
	—3.97 (s)	Cl	—1.73 (v)
CF ₃	—2.6 (s)		—1.55 (s)
NH ₂	+1.53 (s)	Br	—1.71 (v)
N(CH ₃) ₂	+1.58 (s)		—1.52 (s)
NO ₂	—4.24 (v)	I	—1.50 (v)
	—3.95 (s)		—1.30 (s)

TABLE 35-2. Average Bond Moments^a

Bond	Moment	Bond	Moment	Bond	Moment
+ —		+ —		+ —	
H—C	0.30	C—Cl	1.56	C—S	0.95
H—C _{Ar}	0.30	C—Cl(2 Cl)	1.20	C=S	2.80
H—N	1.31	C—Cl(3 Cl)	0.85	C—N	0.40
H—O	1.53	C _{Ar} —Cl	1.43	N—C _{Ar}	0.52
H—S	0.68	C—Br	1.48	C=N	0.90
H—F	1.98	C _{Ar} —Br	1.41	C≡N	3.60
H—Cl	1.03	C—I	1.29	N—O	0.30
H—Br	0.78	C _{Ar} —I	1.20	N=O	2.0
H—I	0.38	C—O	0.86	N→O	3.2
C—F	1.51	O—C _{Ar}	0.47	S→O	2.5
C _{Ar} —F	1.27	C=O	2.40		

^a C. C. Price, *Mechanism of Reactions at Carbon-Carbon Double Bonds*, Interscience, New York (1946), p. 14. By permission of the publisher.

Dipole moments of compounds in solution differ slightly in value from those obtained in the vapor state. The solvent can interact with polar molecules in several ways, most of which tend to decrease dipole moments.

Some average group dipoles for groups on the benzene ring are given in Table 35-1. In using these moments for calculations, hydrogen moments are taken as zero.

Positive values for the group moment indicate that the group is positive with respect to the benzene ring; negative that the group is negative with respect to the ring.

Average bond moments are given in Table 35-2. Except for those marked "Ar," such moments apply only in compounds without resonance. Hydrogen moments must be computed when using these values.

SUPPLEMENTARY READINGS

- Ferguson, L. N., *Electron Structures of Organic Molecules*, Prentice-Hall, Englewood Cliffs, N. J., 1952, pp. 122-133 and 178-185.
- Glasstone, S., *Textbook of Physical Chemistry*, 2nd Ed., Van Nostrand, Princeton, N. J., 1946, pp. 543-556.
- Ingold, C. K., *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, pp. 94-108.
- Leermakers, J. A., and A. Weissberger, "Constitution and Physical Properties of Organic Compounds," *Organic Chemistry II*, Wiley, New York, 1943, pp. 1752-1760.
- McClellan, A. L., *Tables of Experimental Dipole Moments*, Freeman, San Francisco, 1962.
- Waters, W. A., *Physical Aspects of Organic Chemistry*, Van Nostrand, Princeton, N. J., 1950, pp. 74-99.

QUESTIONS AND PROBLEMS

1. Calculate the bond angles of the central atoms in the following compounds from the observed dipole moments and the group moments given in Table 35-1 or Table 35-2.

- | | |
|--|---------------------------------|
| a. diphenylmercury, $\mu = 0$ | 0.4 (use values for moments in |
| b. triphenylamine, $\mu = 0$ | solution) |
| c. <i>p,p'</i> -dibromodiphenyl ether, $\mu =$ | d. trimethylamine, $\mu = 0.67$ |

2. Show clearly what is meant by each of the following terms. Accompany diagrams with verbal explanation.

- | | |
|------------------------|-----------------------|
| a. bond moment | e. group moment |
| b. dielectric constant | f. molar polarization |
| c. dipole | g. nonpolar molecule |
| d. dipole moment | h. polar molecule |

3. Show which of the isomers in the following isomer pairs with μ_1 and μ_2 are *cis*, which *trans*. Calculate the dipole moment of each isomer from the group or bond moments.

- | | |
|--|---|
| a. 1,2-dichloroethane, $\mu_1 = 0$,
$\mu_2 = 1.8$ | d. 2,3-dichloro-2-butene, $\mu_1 = 0$,
$\mu_2 = 3.03$ |
| b. 2-butene, $\mu_1 = 0$, $\mu_2 = 0.5$ | e. 1-chloro-1-propene, $\mu_1 = 1.71$,
$\mu_2 = 1.97$ |
| c. β -bromostyrene, $\mu_1 = 1.24$,
$\mu_2 = 1.53$ | |

4. Discuss the idea that because methane is nonpolar, the hydrogen atom and methyl group have identical group moments in all hydrocarbons and their derivatives. What data seem to confirm this notion? What data refute it? What is the real reason for nonpolarity in a polyatomic molecule?

5. Under what circumstances do bond moments or group moments deviate significantly from their average values?

6. Explain how symmetrical molecules such as hydroquinone, 1,2-dichloroethane, and *trans*-1,4-dibromo-2-butene can be polar.

7. Discuss the problem of the calculation of average dipole moments of molecules whose polar groups are separated by many carbon atoms in a flexible chain. Explain why use of dipole moments to determine *cis* and *trans* isomers is practical only for relatively simple molecules.

36

Diffraction

36-1 THEORY OF DIFFRACTION

Diffraction is a wave reinforcement phenomenon. Waves reflected from several points may recombine in phase, at opposite phase, or partly out of phase (Fig. 36-1).

The way the waves recombine after passing through a diffraction grating (a series of reflecting points or lines) depends on the angle at which the waves strike the grating and the distance between the grating points (Fig. 36-2). For reinforcement to occur, the extra distance, abc (in Fig. 36-2C),

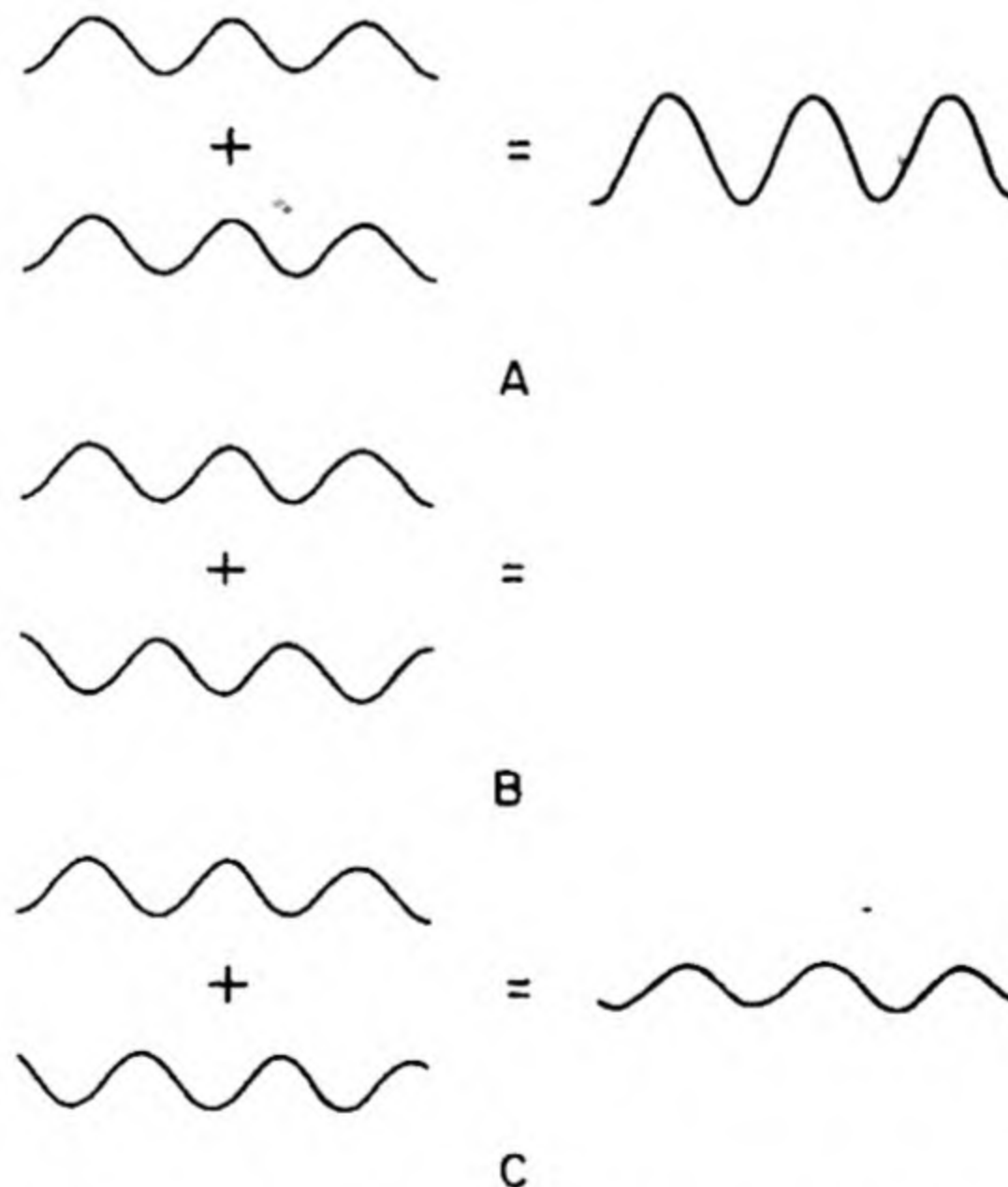


Fig. 36-1. Combination of Waves at Different Phases. (A) In phase: reinforcement. Phase separation = 0 radians. (B) Opposite phase: cancellation. Phase separation = π radians. (C) Partly out of phase. Phase separation between 0 and π .

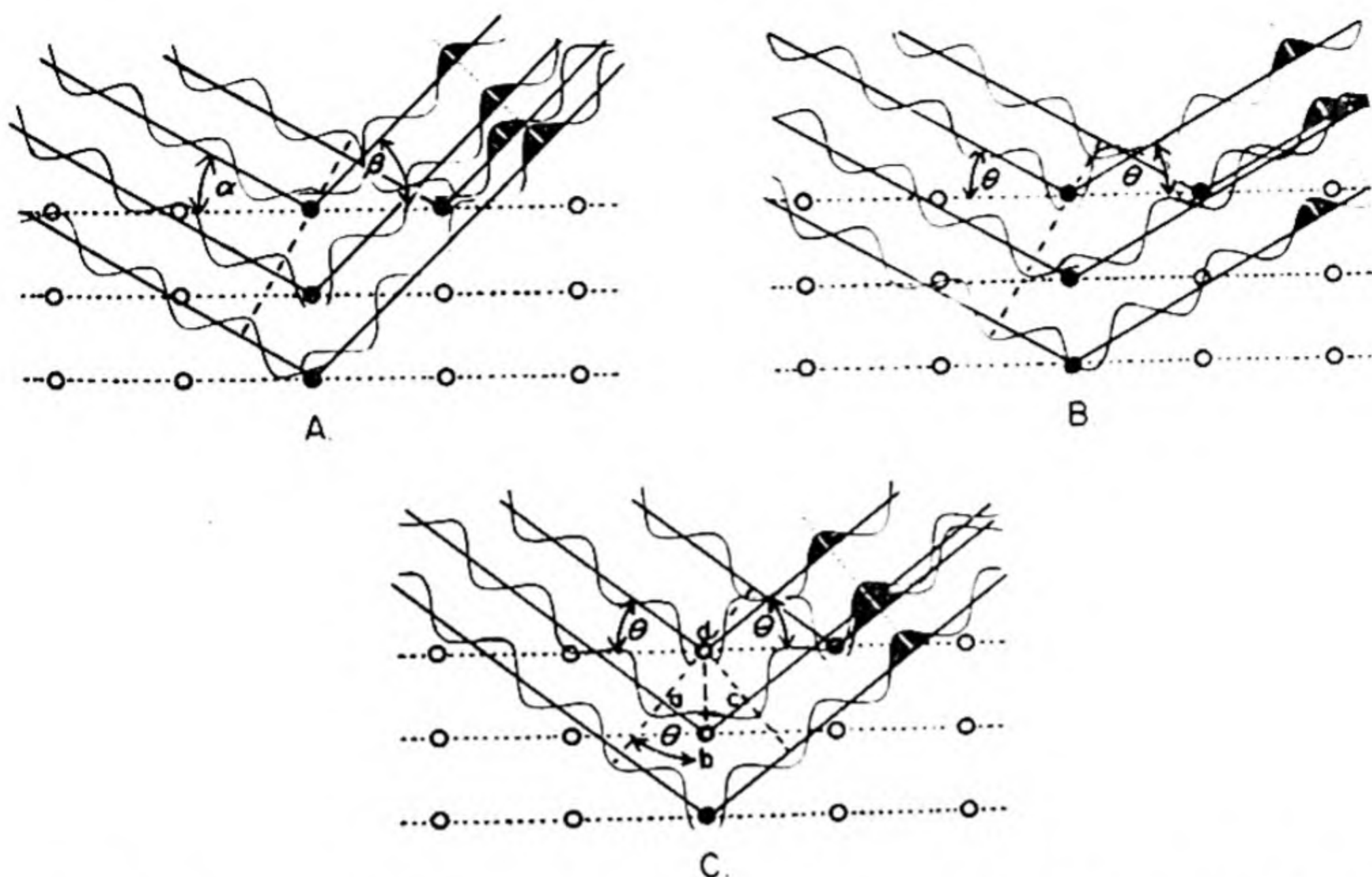


Fig. 36-2. Diffraction of Waves from Points in a Grating. (A) $\alpha \neq \beta$; even when waves scattered from one column of atoms are in phase, those from different columns are generally out of phase. (B) $n\lambda \neq 2d \sin \theta$; all scattered waves out of phase. (C) All scattered waves in phase.

traversed by each wave beyond that traversed by the next superior wave must be exactly a whole number of wavelengths. The relationship between wavelength and distance, bd , between grating points is thus given by the Bragg equation (eq. 1)

$$(1) \quad n\lambda = 2(bd) \frac{ab}{bd} = 2d \sin \theta$$

where n is an integer; λ the wavelength, and d the grating distance (bd in Fig. 36-2C) in the same units. When the grating is made up of atoms, with grating distances in the order of 10^{-8} cm., electromagnetic waves of similar magnitude must be used for diffraction. Thus, the waves must be at least as short as x-rays (see Fig. 33-1).

When the points from which the waves are reflected are evenly spaced, a series of spots is obtained on a photographic plate in position to receive the reflected beams. These spots correspond to reinforcement beams obtained at angles such that abc (Fig. 36-2C) equals one, two, three, etc. whole wavelengths. Also, in a three-dimensional grating, other distances are involved, such as diagonals of squares and diagonals of cubes. The sum of all these spots is the diffraction pattern obtained from uniform, crystalline materials (Fig. 36-3A).

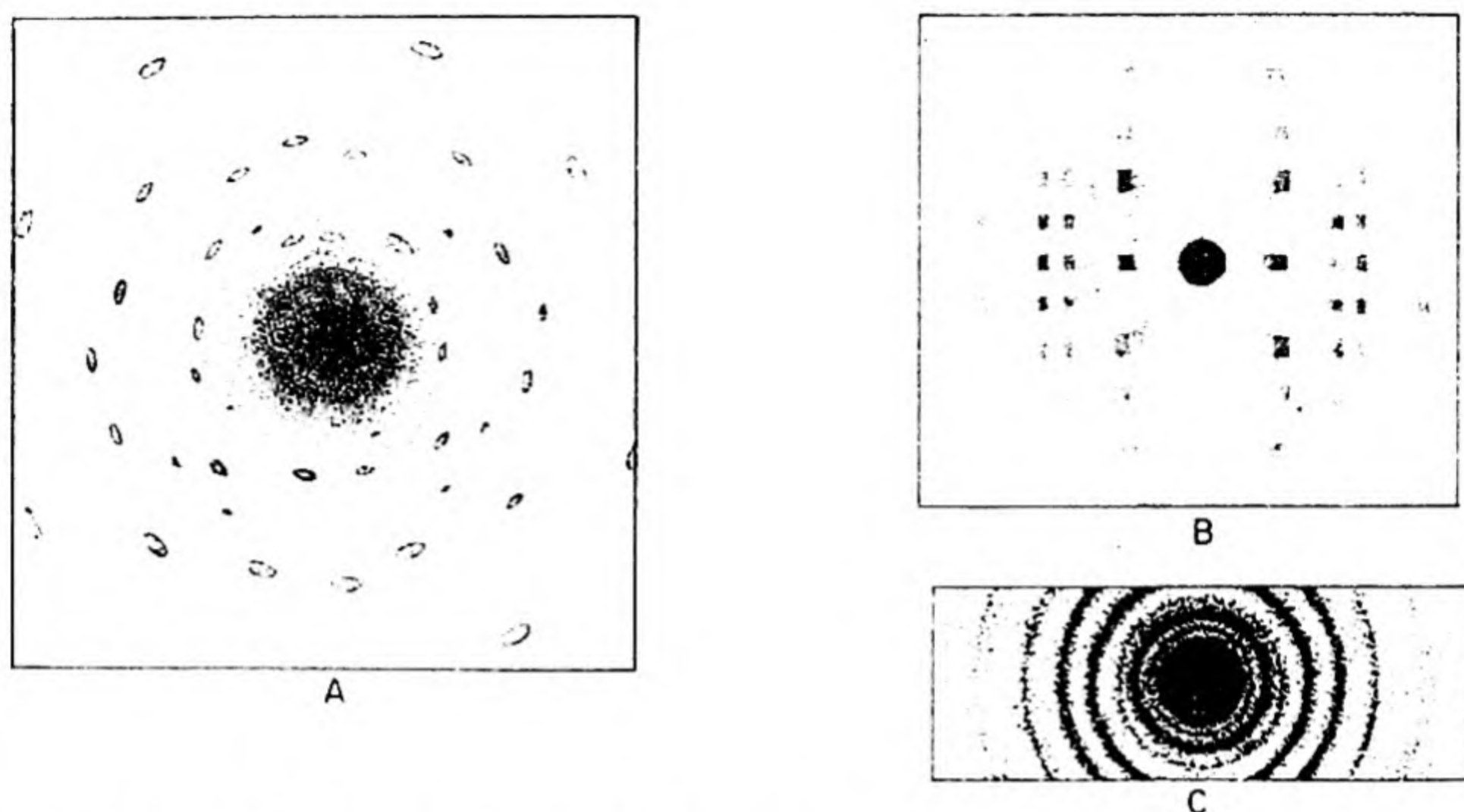


Fig. 36-3. Diffraction Patterns. (A) Laue crystal photograph of magnesium oxide, (B) Rotation pattern of crystalline benzil, (C) Typical liquid diffraction pattern. (Parts (A) and (B) from Glasstone's *Textbook of Physical Chemistry*, Copyright 1946, D. Van Nostrand Company, Inc., Princeton, N. J.)

Organic molecules, however, involve many different interatomic distances, even in the crystalline state. Furthermore, it is impractical to solidify all organic compounds to obtain their diffraction patterns.

In fluids, molecules are oriented in all possible directions and present all possible grating distances. It would at first appear hopeless, therefore,

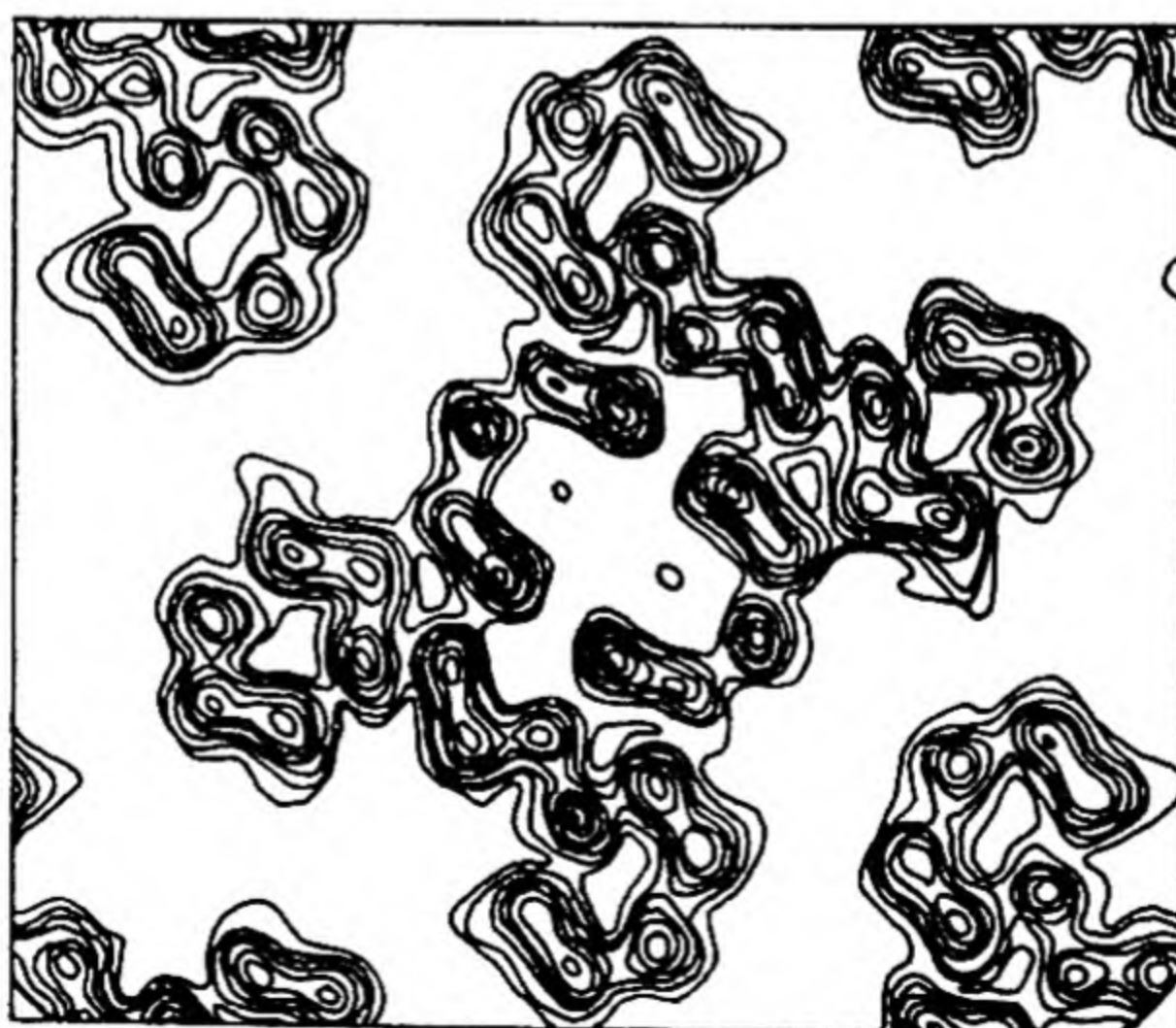


Fig. 36-4. Oscilloscope Electron Density Contour Map of Phthalocyanine, Using X-Ray Analog Computer (X-RAC).

to expect any kind of diffraction pattern from a liquid or gas. However, there are regularities even in the random orientations of molecules, which appear as diffraction patterns. Since the molecules are oriented in all directions to the incident beam, the diffraction pattern is a series of concentric circles (Fig. 36-3C) instead of spots. From such data it is often possible to compute the structures of molecules. Some electron density plots obtained by computer and by photographic analysis are shown in Figs. 36-4 and 36-5.

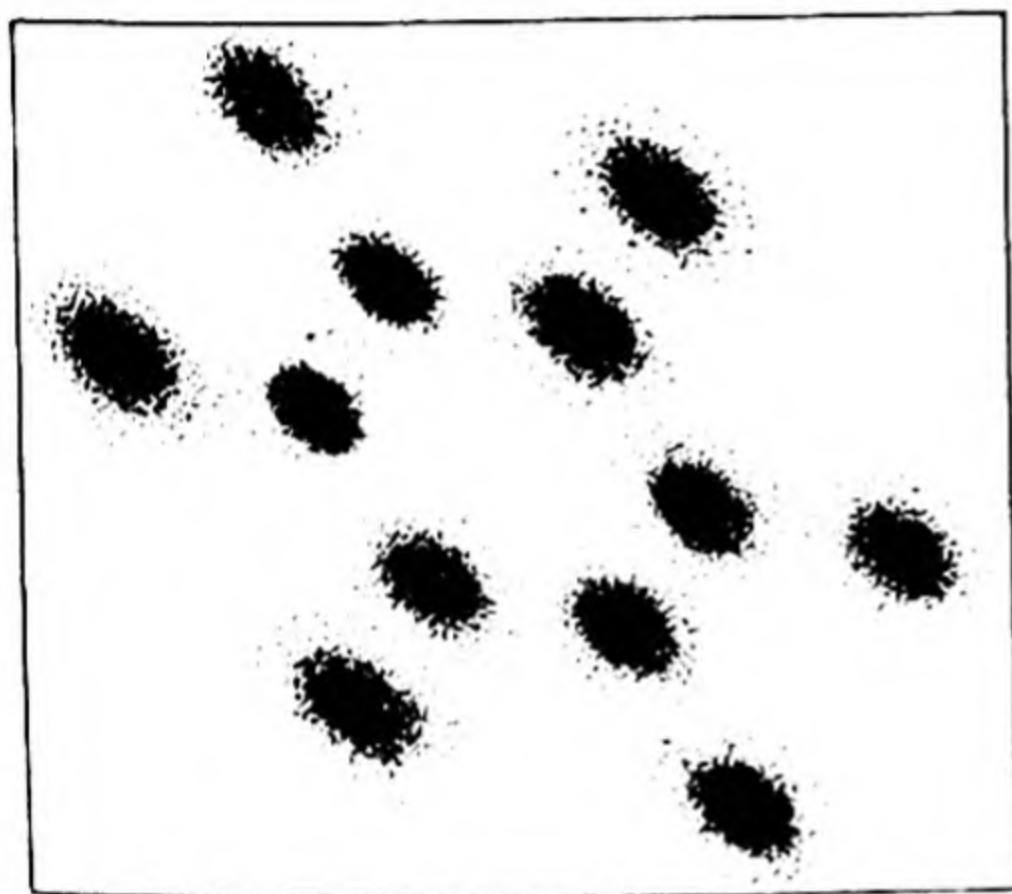


Fig. 36-5. Projection of Hexamethylbenzene by Bragg-Huggins Photographic Summation.

36-2 DIFFRACTION TECHNIQUES

Three types of radiation are presently utilized for diffraction studies. These are x-rays, electron beams, and neutron beams.

A. X-Ray Diffraction

X-rays are most successfully used with heavier elements, which give more intense diffraction, hence clearer patterns. One of the deficiencies of the use of x-rays is their inability to locate hydrogen atoms in large molecules. This is partly a problem of wavelength, partly one of electron density.

Another limitation of x-rays is their inability to be focused. This prevents their use in any kind of device which might resolve the diffraction pattern into an image of the grating.

It is of interest to stereochemistry that scattering of x-rays near absorption maxima of atoms is anomalous and makes possible clear distinctions between those elements involved in the absorption and others. Such an anomalous pattern for an asymmetric molecule in the crystalline state is asymmetric. Thus, in 1951 Bijvoet and his associates were able to establish the absolute configuration of D-sodium rubidium tartrate by

using x-rays absorbed by the rubidium and applying a quantum-mechanical evaluation of the scattering pattern. This determination established the Fischer convention of relative configurations of sugars as the correct absolute configurations.

B. Electron Diffraction

Electron beams have been used to determine the structures of gaseous molecules. The advantage of electron beams is that an electron beam can be focused, or collimated, by annular magnets. Electrons are affected by atomic nuclei as well as orbital electrons. This enables electrons to locate hydrogen atoms in molecules which do not have many heavy atoms. One distinct disadvantage of electron beams is that their use is confined to gases, vapors, and very thin sections of solids.

C. Neutron Diffraction

Neutron beams, provided generally by bombardment of beryllium with high speed alpha particles, have also been used to some extent for diffraction studies. The difficulty and expense inherent in providing the neutrons and technical difficulties of handling and detecting neutrons have limited their usefulness.

SUPPLEMENTARY READINGS

- Clark, G. L., and E. Wolthuis, "A Resume of Electron Diffraction," *J. Chem. Educ.* **15**, 64-75 (1938).
 Glasstone, S., *Textbook of Physical Chemistry*, 2nd Ed., Van Nostrand, Princeton, N. J., 1946, pp. 355-375, 399-407, 591-596.
 Robertson, J. M., *Organic Crystals and Molecules*, Cornell University Press, Ithaca, N. Y., 1953.
 Ryland, A. L., "X-Ray Diffraction" (of polymers), *J. Chem. Educ.* **35**, 80-83 (1958).

QUESTIONS AND PROBLEMS

1. Give an explanation, illustration, or definition to show clearly what is meant by each of the following terms. Accompany diagrams with verbal explanation.
 - a. diffraction
 - b. diffraction pattern
 - c. reinforcement
2. Why can electron diffraction provide accurate information only about relatively simple compounds?

37

Mass Spectra

37-1 POSITIVE ION BEAMS

The principle of the mass spectrograph has already been introduced in the basic chemistry course. There it was presented as a means of separating, detecting, and identifying isotopes. For this purpose, elements (generally metallic) are injected into an electrical field which ionizes them, and the resulting beam of positive ions is passed through a focusing magnetic field onto a detector. Ions of identical mass/charge ratio arrive at the same point; those of different masses are distributed accordingly (see Fig. 37-1).

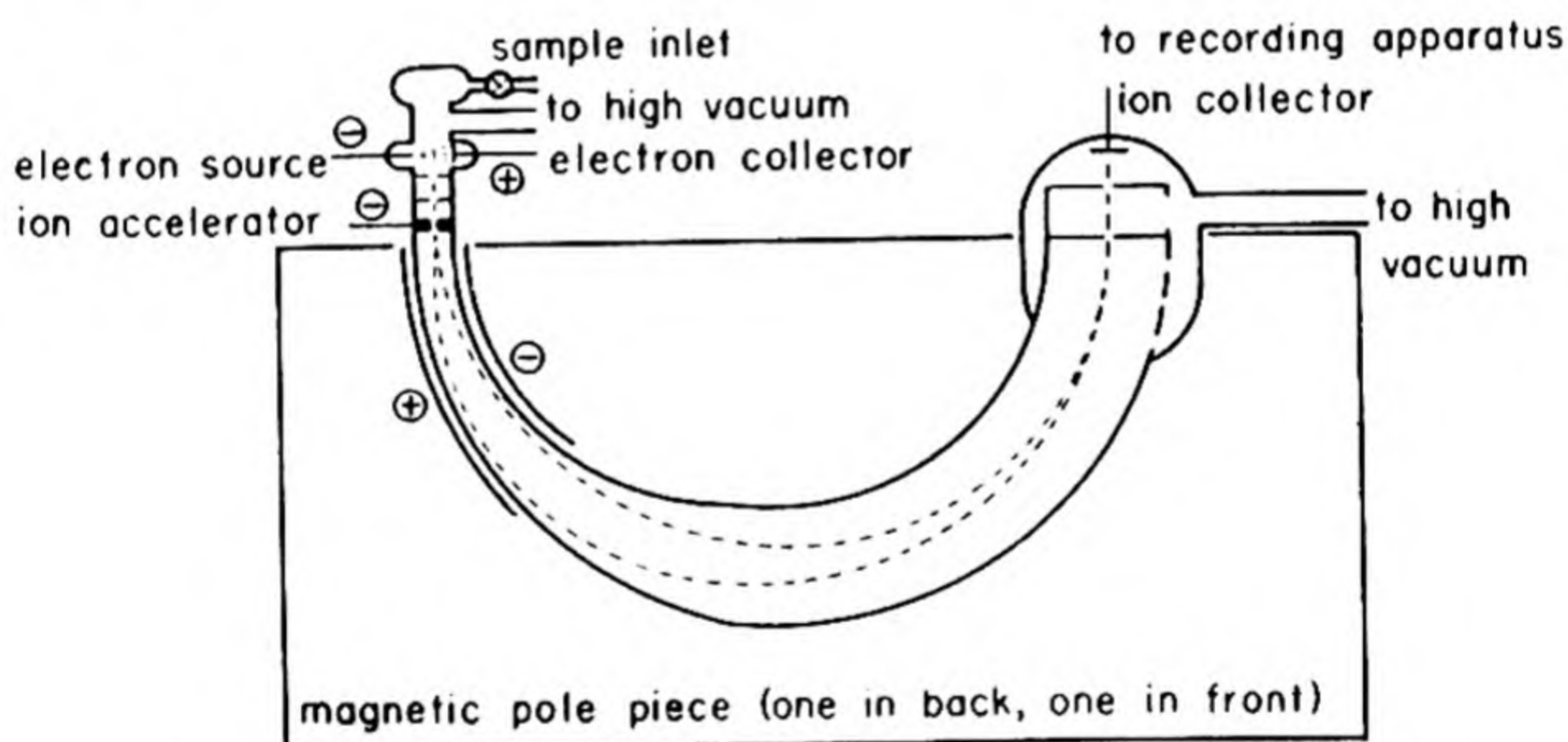
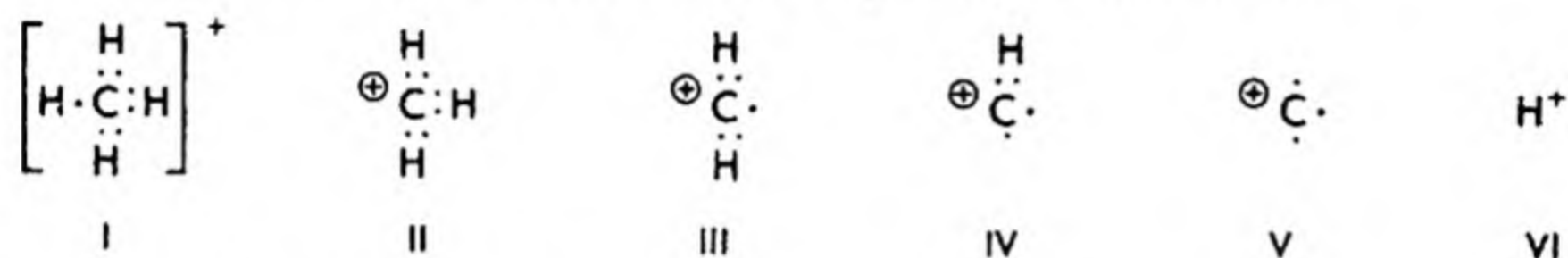


Fig. 37-1. Schematic Diagram of a Mass Spectrometer.

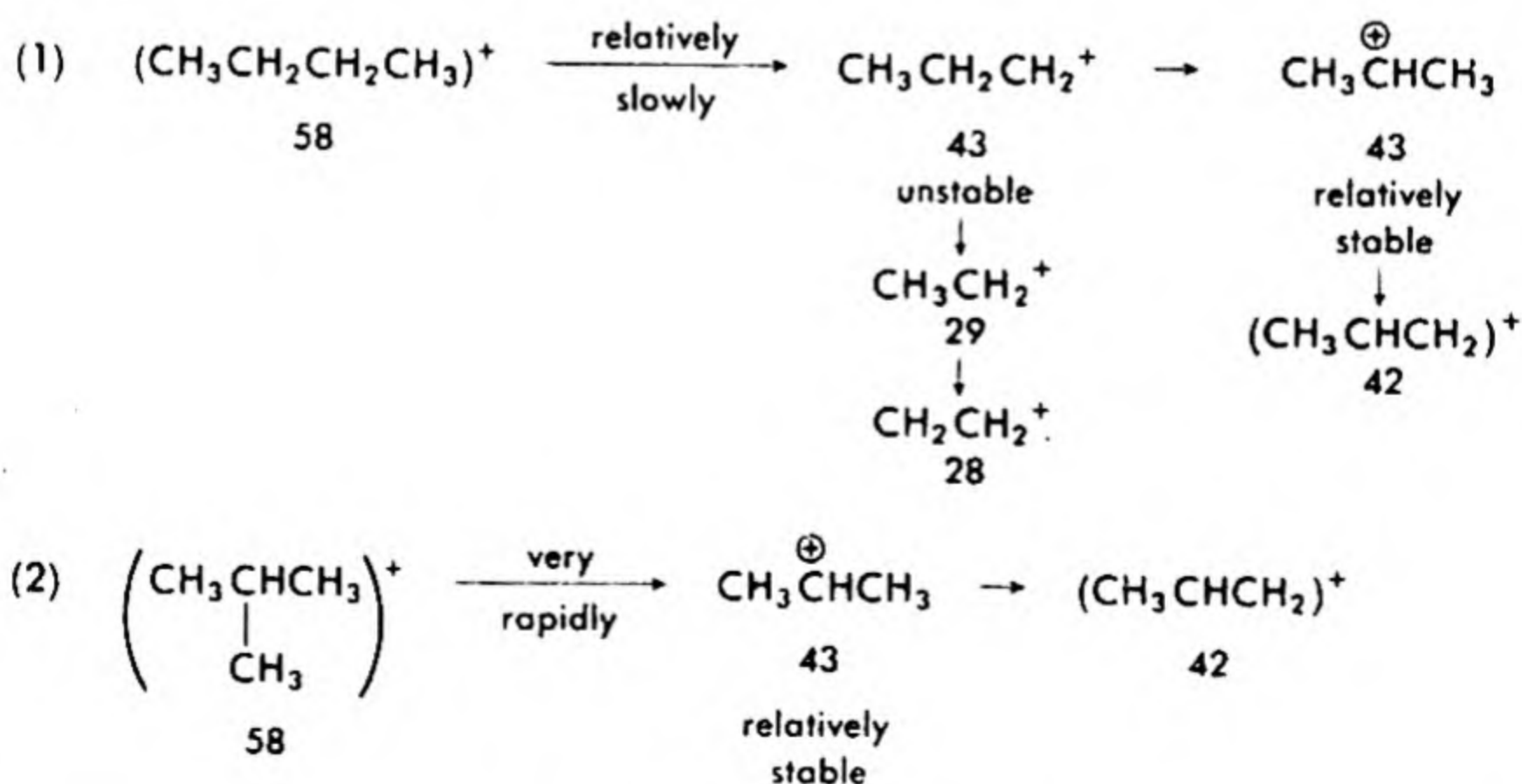
There is no reason to limit the use of mass spectra to atoms; molecules can also be ionized and the masses of the component ions identified by their positions at the detector. Thus, in 1940 mass spectra of molecules began to provide an important method for analyzing mixtures of compounds. More recently, data from mass spectra have provided information about the ionization energies of molecules. Such data are often helpful to an understanding of reaction mechanisms.

37-2 MOLECULAR MASS SPECTRA

While atoms are not disintegrated by ionization energies, molecules generally are, so that one molecule gives a number of particles with masses ranging from that of the whole molecule downward. For example, methane gives particles of mass 16 (I), 15 (II), 14 (III), 13 (IV), 12 (V), and 1 (VI) in proportions which depend on the relative stabilities of the ions. Doubly and triply charged ions may contribute to the spectra if ionizing energies of the apparatus are sufficiently high, but ordinarily low-energy bombardments by electrons provide only singly charged ions. In addition to the masses listed as resulting from methane, small amounts of mass 17 and mass 2 are detected due to ^{13}C and ^2H . Such strange species as I, III, IV and V, are found because of the very small number of collisions between particles in the very low pressure used.



The relative abundance of ions from methane (I:II:III:IV:V = 1:0.876:0.183:0.087:0.029) constitutes its characteristic "spectrum" (which varies only slightly with changes in instrumentation). Since a mass spectrum depends on the relative stabilities of the ions, together with their rate of formation by cleavage of heavier ions, slight changes in molecular structure produce significant changes in the spectrum. Thus, butane and isobutane differ very significantly in the relative abundances of particles of mass 58, 42, 29, and 28:



Thus, the relative abundances of these masses for butane and isobutane are those given in Table 37-1. Subtle differences occur between other mass abundances.

TABLE 37-1. Striking Differences in Mass Spectra between Butane and Isobutane

Mass	Relative Abundance	
	Butane	Isobutane
58	12.85	0.316
43	100.0	112.3
42	12.20	3.63
29	3.67	0.658
28	2.73	0.296

Certain positive ion abundances are related to certain structural features, so that mass spectra can be used to provide structural evidence. Mass spectra can also be used for the analysis of mixtures.

37-3 MOLECULAR IONIZING ENERGIES

Since a molecule can be ionized only when it is struck by an electron energetic enough to ionize one of its electrons, the threshold energy for obtaining a mass spectrum is a measure of the ionizing potential of the molecule. From this information and the relative abundances of cleavage product ions can be deduced the energies of such reactions as (4) through (7) (see Fig. 37-2).

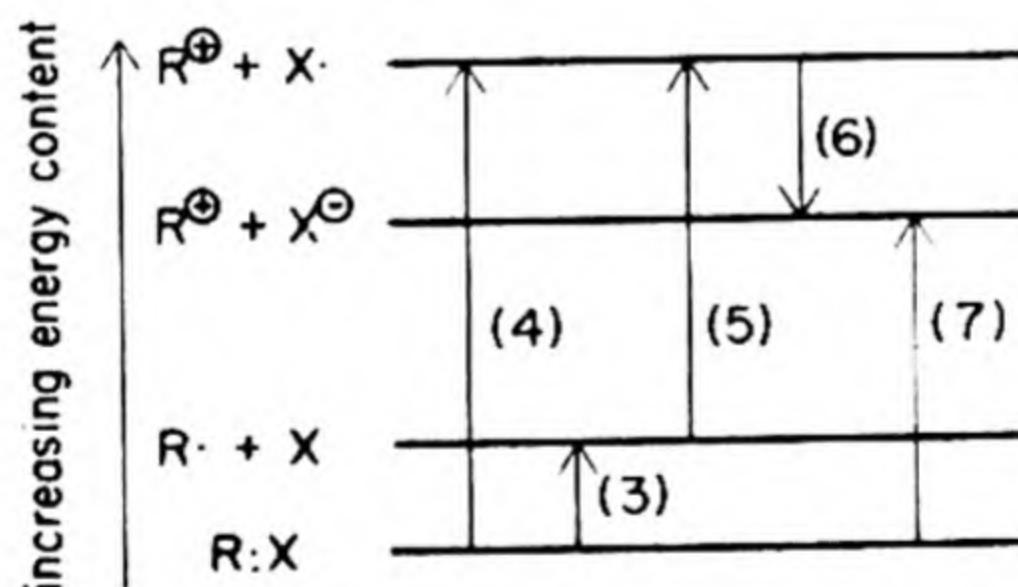
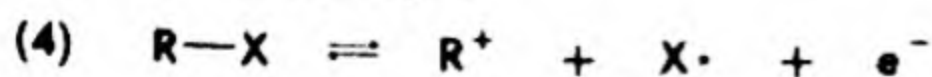


Fig. 37-2. Energy relationships for eqs. (3) through (7).

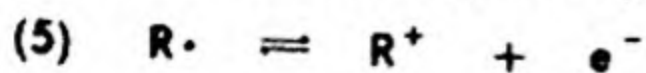
Homolytic dissociation (independently determined):



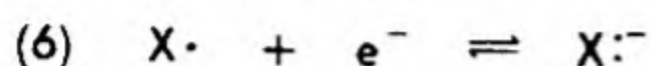
Ionization cleavage:



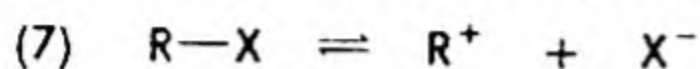
Radical ionization (from eqs. 3 and 4):



Radical ionization:



Heterolytic dissociation (from eqs. 4 and 6 or 3, 5, and 6):



37-4 HIGH RESOLUTION MASS SPECTROSCOPY

In the early 1960's, high resolution mass spectrometers became available to organic chemists. These are capable of determining masses of ionic fragments to three decimal places. In an ordinary mass spectrometer, for example, C_2H_4 (mass 28.040), N_2 (mass 28.015), and CO (mass 28.003) all appear at the same position, that is, their peaks are not resolved. In a high resolution instrument, these are resolved. In this way, but of course with larger fragments, it is now possible to determine the carbon, hydrogen, oxygen, nitrogen analysis of fragments of molecules (other elements may also be included), and whole structures of complex organic molecules may often be deduced from such data.

SUPPLEMENTARY READINGS

- Beynon, J. H., *Mass Spectroscopy and its Applications to Organic Chemistry*, Elsevier, Amsterdam, 1960.
- Biemann, K., *Mass Spectroscopy*, McGraw-Hill, New York, 1962.
- Budzikiewicz, H., C. Djerassi, and D. H. Williams, *Interpretation of Mass Spectra of Organic Compounds*, Holden-Day, New York, 1964.
- Budzikiewicz, H., C. Djerassi, and D. H. Williams, *Structure Elucidation of Natural Products by Mass Spectroscopy*, Holden-Day, New York, 1964.
- Ewing, G. W., *Instrumental Methods of Chemical Analysis*, 2nd Ed., McGraw-Hill, New York, 1960, Chapter 15.
- McLafferty, F. W., ed., *Mass Spectroscopy of Organic Ions*, Academic Press, New York, 1963.
- Willard, H. H., L. L. Meritt, and J. A. Dean, *Instrumental Methods of Analysis*, 3rd Ed., Van Nostrand, Princeton, N. J., 1958, Chapter 10.

PROBLEMS

1. In mass spectra of alkanes, masses of 29 (propanes and higher), 43 (butanes and higher), 57 (hexanes and higher), 71 (heptanes) etc. are generally among the more abundant masses. Explain by outlines such as (1) and (2) why masses 57, 43, and 29 should be abundant in spectra of hexane and 2,2-dimethylbutane.
2. Masses 57 and 29 are anomalously low in the mass spectrum of 2,3-dimethylbutane. Show what this means regarding the cleavages of this molecule.

UNIT



Topics of Special Interest

38

Carbohydrates

38-1 CARBOHYDRATES

A carbohydrate is a polyhydroxy carbonyl compound, a compound which produces such a material on hydrolysis, or a closely related derivative. The usual type formula for a carbohydrate is $C_n(H_2O)_m$, whence the name. However, there are exceptions to this formula, notably deoxy sugars.

A. Classification

Carbohydrates are categorized according to the number of separate carbon chains per molecule. The simplest are *monosaccharides*, in which one continuous chain of carbon atoms makes up the backbone of the molecule. *Disaccharides* yield two monosaccharide units per molecule upon hydrolysis. The two carbon chains are linked through an oxygen atom. *Oligosaccharides* are those carbohydrates constituted of two to six monosaccharide units. This term thus includes disaccharides, trisaccharides, etc., to hexasaccharides. Monosaccharides, disaccharides, and lower oligosaccharides are often termed sugars.

Polysaccharides are those carbohydrates which, upon hydrolysis, yield a large number of monosaccharide or disaccharide units per molecule.

B. Monosaccharides

(1) *Classification.* Two factors are embodied in the classification of monosaccharides: the number of carbon atoms in the chain and the type of carbonyl function. Prefixes tri, tetra, etc., are used to designate the number of carbon atoms per molecule. The suffix, *-ose*, is a general designation of a carbohydrate. A triose, for example, is a monosaccharide containing three carbon atoms in the molecule. Hexoses and pentoses are the most common naturally occurring monosaccharides.

Aldoses are monosaccharides with terminal carbonyl functions; ketoses, those with keto groups. The two classifications are combined in such terms as aldopentoses and ketotriose.

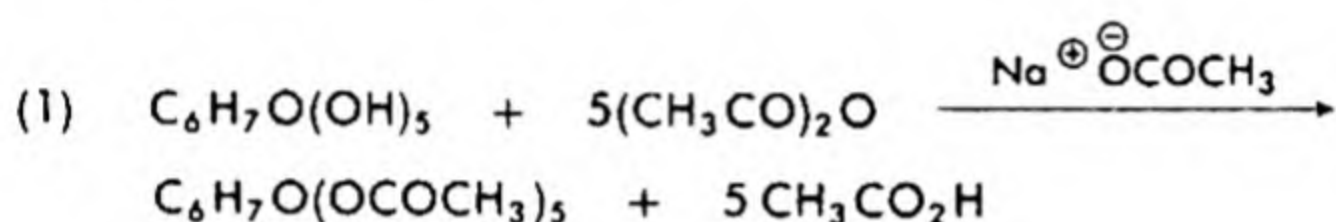
(2) *Physical Properties.* Monosaccharides are crystalline solids, which

ordinarily decompose at or slightly above their melting points. They are highly soluble in water, but virtually insoluble in organic solvents. Many sugars are difficult to isolate and purify because of their tendency to form syrupy, supersaturated solutions. These are properties of highly polar, hydrophilic compounds.

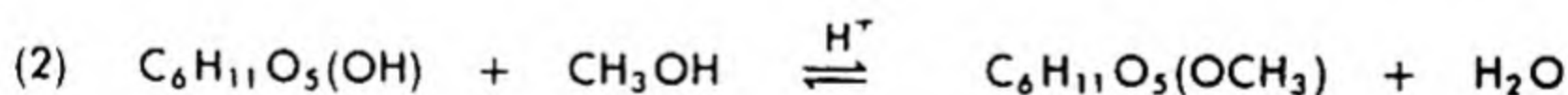
With the exception of the ketotriose, monosaccharides contain asymmetric carbon atoms, hence are optically active.

(3) *Chemical Properties. Glucose as a Typical Monosaccharide.* In considering simple sugars, or monosaccharides, it is useful to discuss glucose as a typical representative. It has the formula $C_6H_{12}O_6$. The fact that it may be isolated from the acid-catalyzed hydrolysis of starch suggests that the carbon atoms in glucose are attached to each other by carbon-carbon bonds rather than by more labile ether bonds (although the existence of the latter in addition to the carbon-carbon bonds is not excluded).

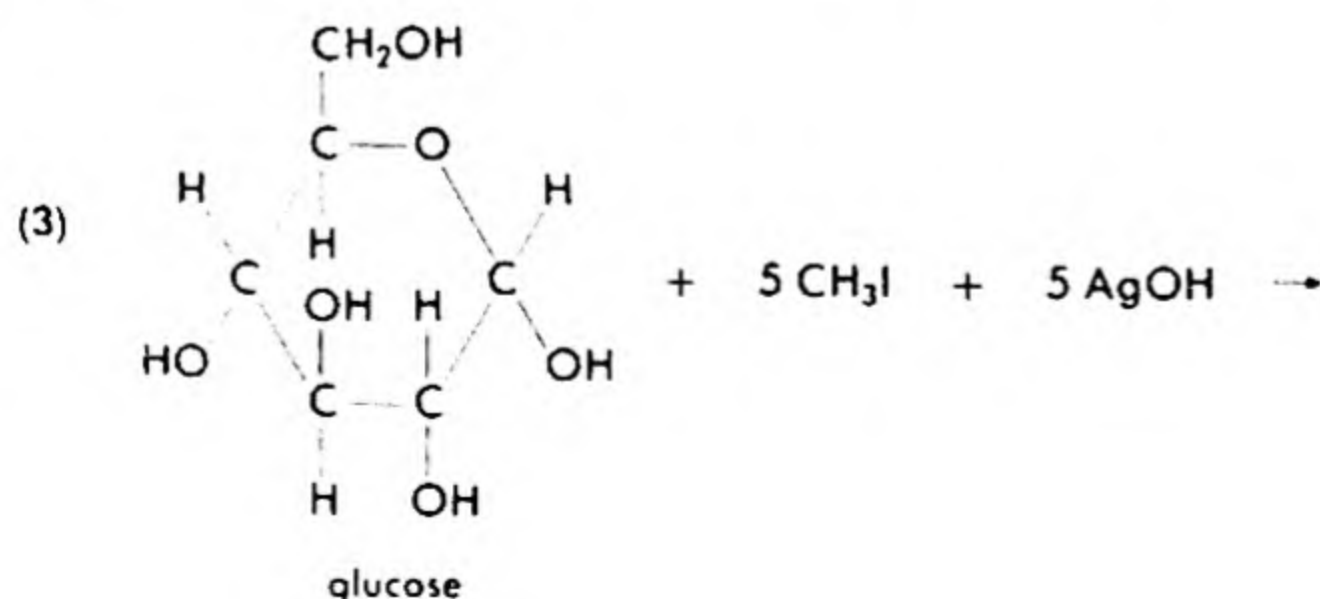
Quantitative acetylation of glucose (or equivalent benzylation) suggests (eq. 1) that there are five hydroxy groups per molecule.

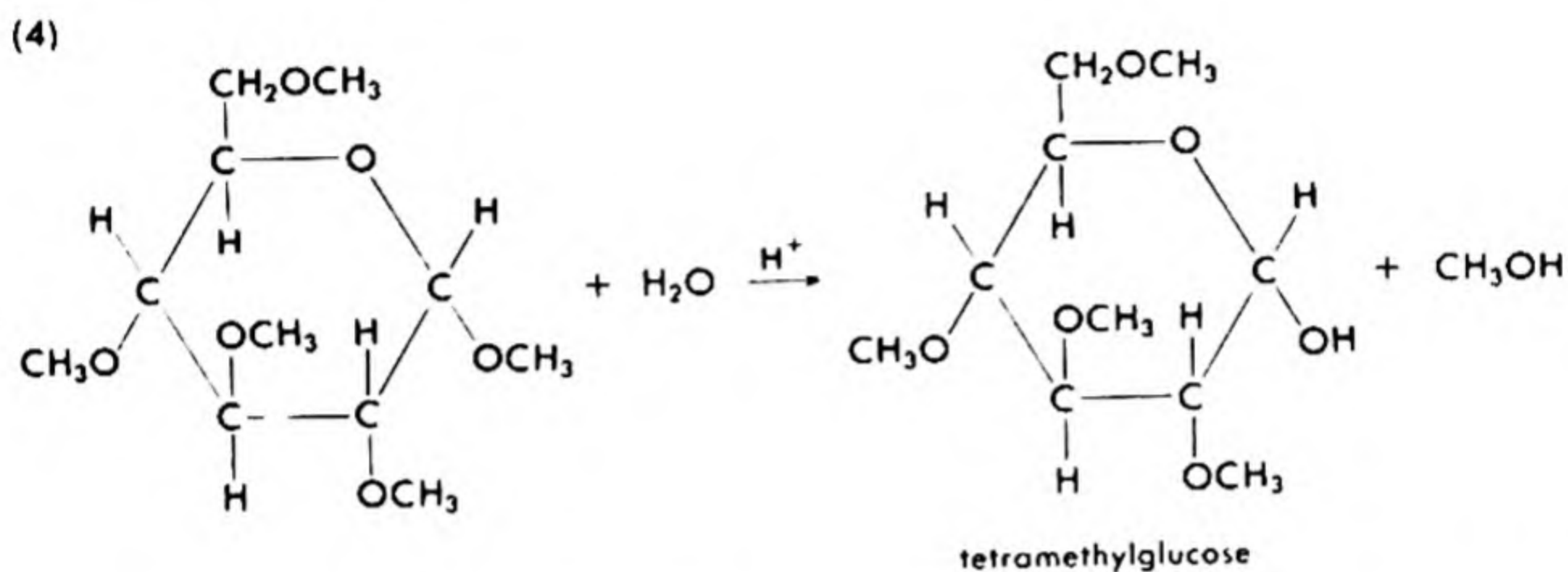
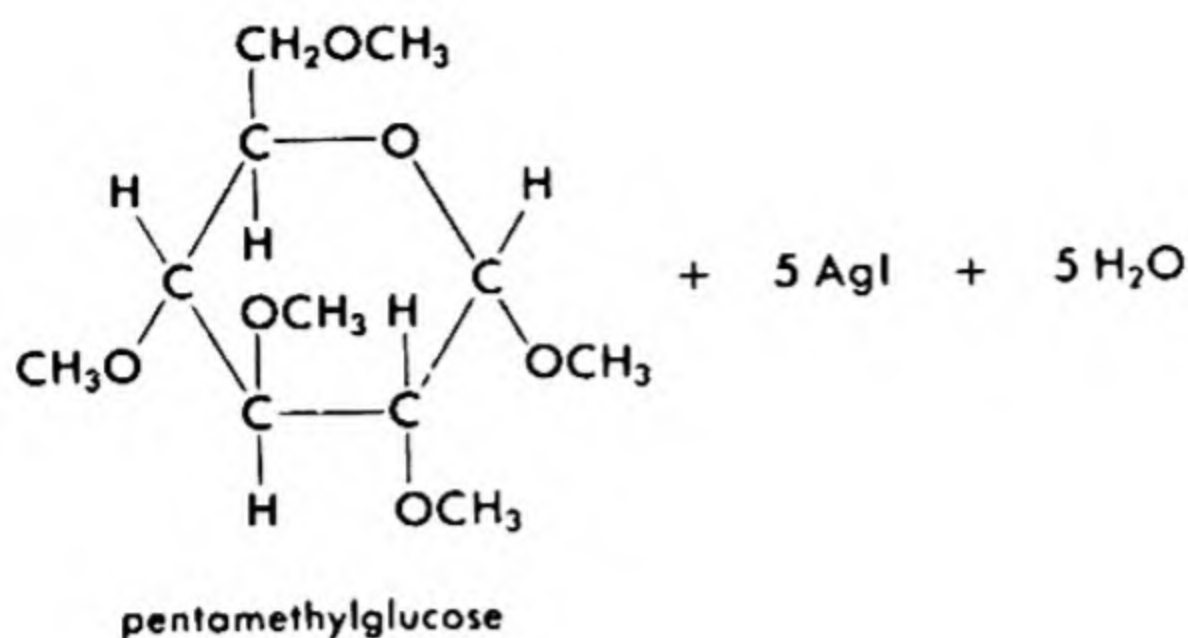


Treatment of glucose with anhydrous methanol in the presence of hydrogen chloride replaces one hydroxy group with a methoxy group. This replacement is readily reversed with dilute aqueous acid, so that the product may be assumed to be an acetal (eq. 2).



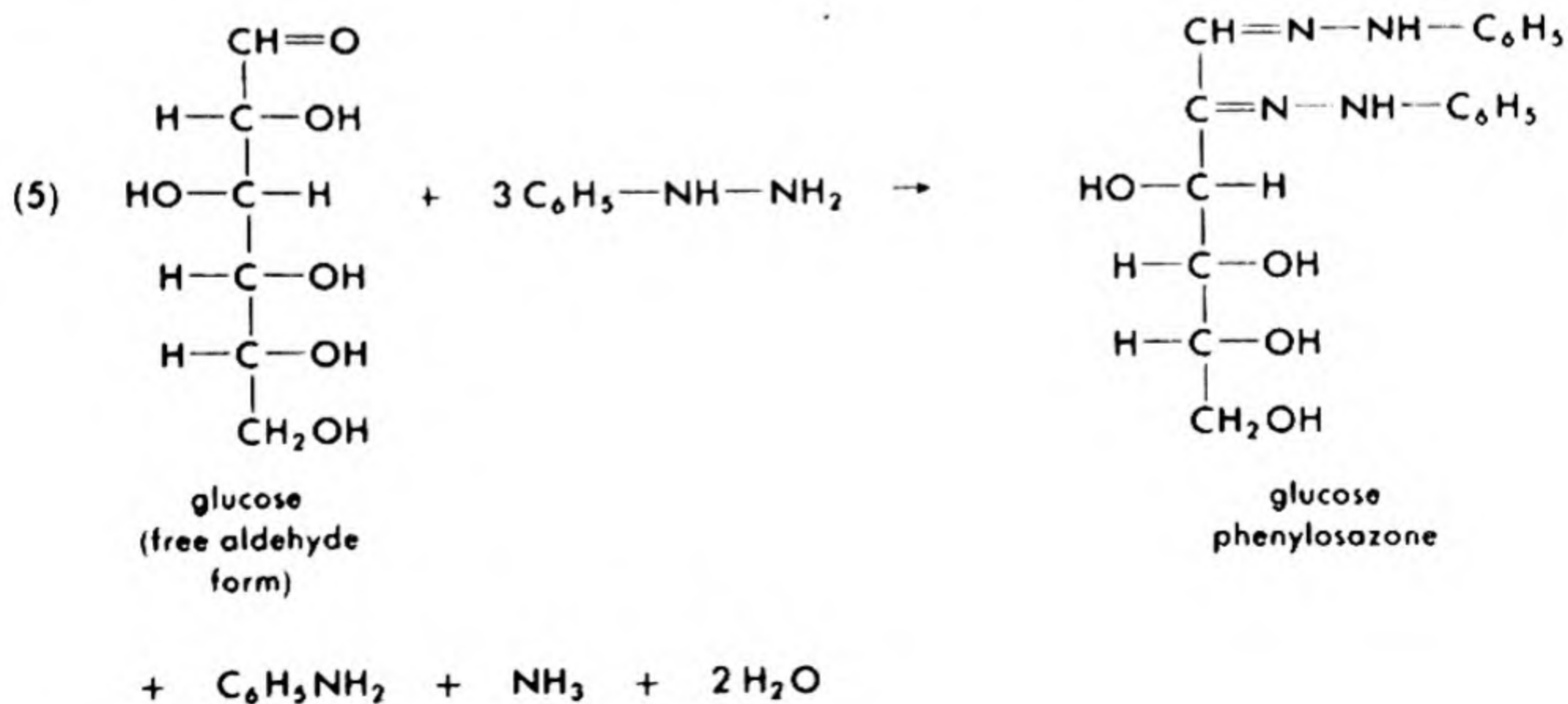
All of the hydroxy groups in the sugar molecule can be methylated by treatment with methyl iodide and silver hydroxide or with methyl sulfate and sodium hydroxide. Of the methyl groups, one, the acetal methyl, is readily removed by hydrolysis. The others are not, hence are ether linkages.



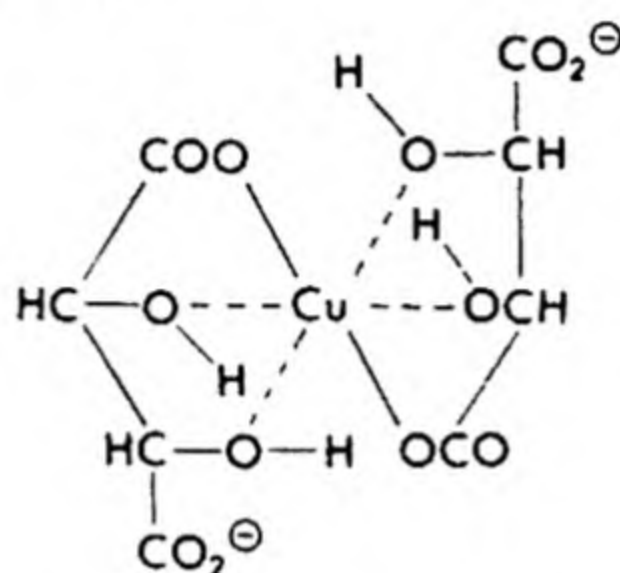


These results show that four of the five hydroxy groups are alcohol groups, while one is a hemiacetal group.

The presence of a carbonyl group (or its equivalent) in glucose is demonstrable by treatment with hydroxylamine. The anticipated oxime is produced. However, treatment of a monosaccharide with phenylhydrazine produces an osazone, a reaction similar to that observed with benzoin (§18-4C). Oxidation occurs only at the hydroxy group adjacent to the original carbonyl group, so that a phenylosazone results (eq. 5).

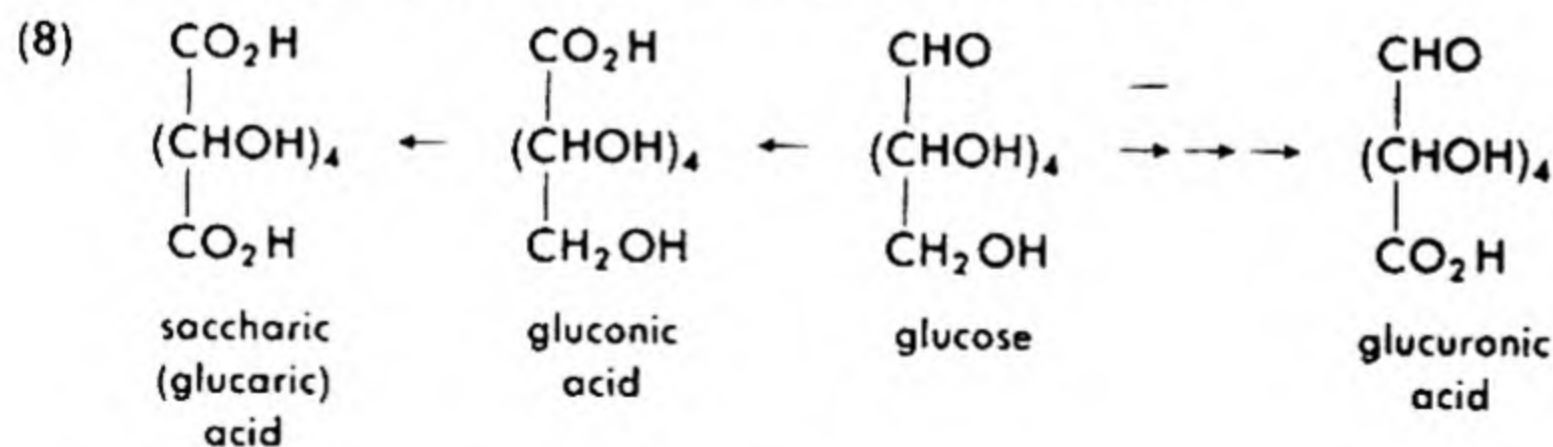
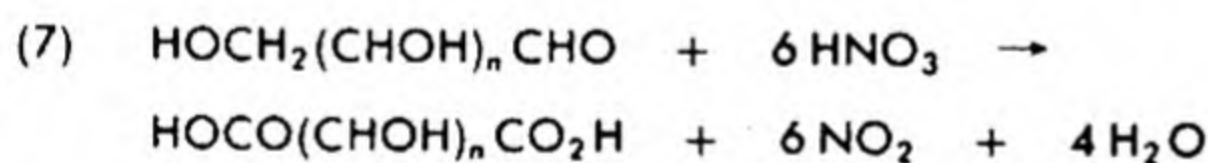
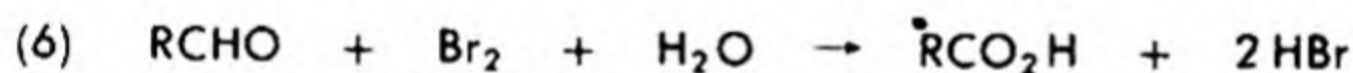


Both aldoses and ketoses are readily oxidized by Fehling's solution and Benedict's reagent. These reagents are important for the determination of free or available carbonyl groups. Both consist of alkaline complexes of cupric ion. Fehling's solution is a mixture of tartratocupric ion and sodium hydroxide. Benedict's reagent is a mixture of citratocupric ion and sodium carbonate. These reagents are reduced to cuprous oxide by α -hydroxyaldehydes and α -hydroxyketones. A positive test is indicated by complete disappearance of color from the solution and the formation of a coral to red-brown precipitate.



one possible representation
of tartratocupric complex

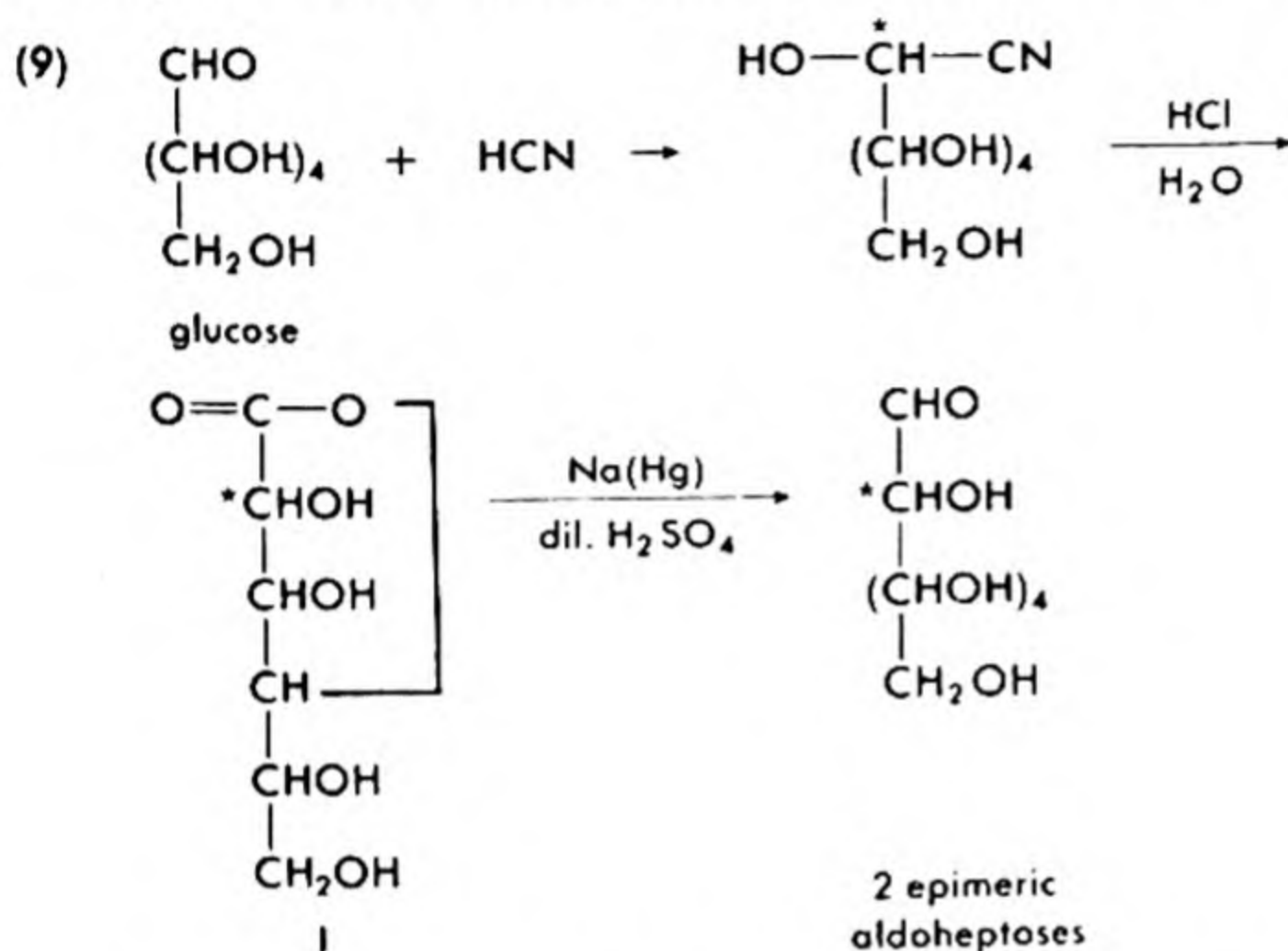
Bromine and dilute nitric acid are reagents useful for oxidation of aldehyde groups of aldoses. The products (eq. 6) are termed *aldonic acids*. Oxidation of an aldose with boiling concentrated nitric acid attacks both the aldehyde group and the primary alcohol group (eq. 7) to give a dicarboxylic acid formerly called a saccharic acid, but now given the generic name *glycaric acid*. The aldehydic acids produced by oxidation of the primary alcohol group are called *glycuronic acids*. This oxidation involves procedures where the other groups susceptible to oxidation are suitably protected and then the protecting substituents are removed later.



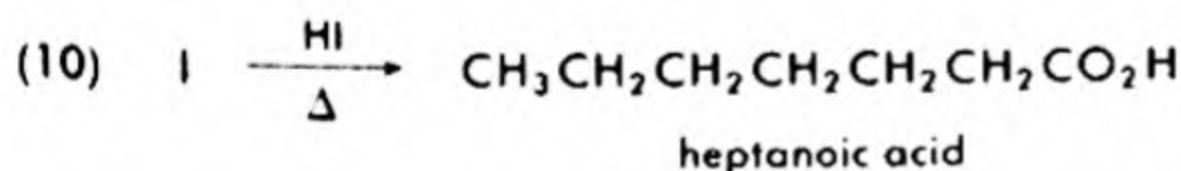
Like simpler aldehydes and ketones, monosaccharides react with hydrogen cyanide to form cyanohydrins. This fact provides a tool effectual in

the structural analysis of monosaccharides, as well as a means of synthesis of aldoses of one more carbon atom per molecule than the original aldose.

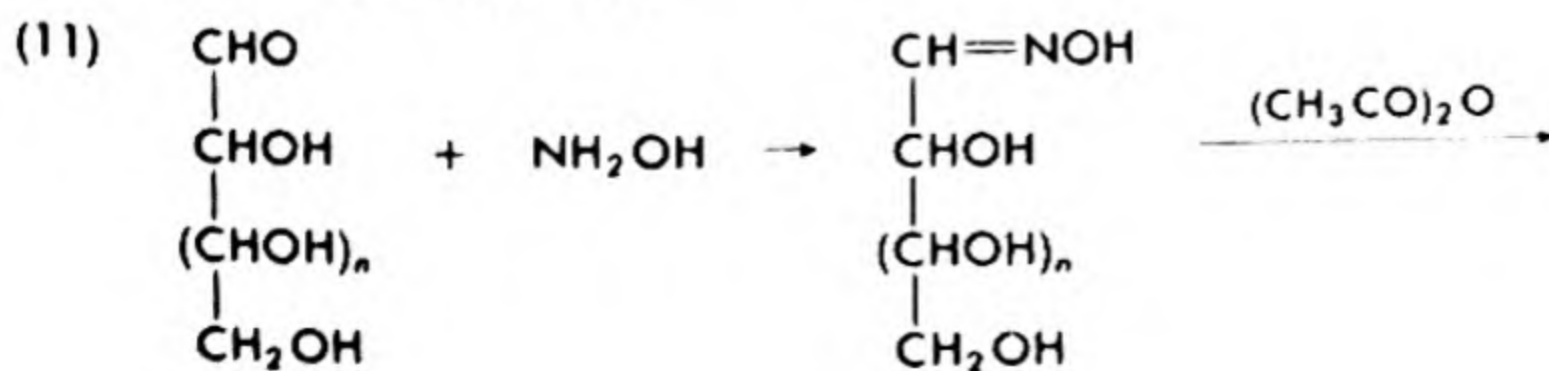
(4) *Interconversions.* Heinrich Kiliani was the first to apply cyanohydrin formation to the synthesis of higher aldoses. The reactions of his method (*Kiliani synthesis*) are summarized in outline (9). The new asymmetric center marked with an asterisk makes possible two product diastereoisomers, which are formed in unequal amounts and differ in configuration at at only one carbon atom (the 2-position). These are called *epimers*.

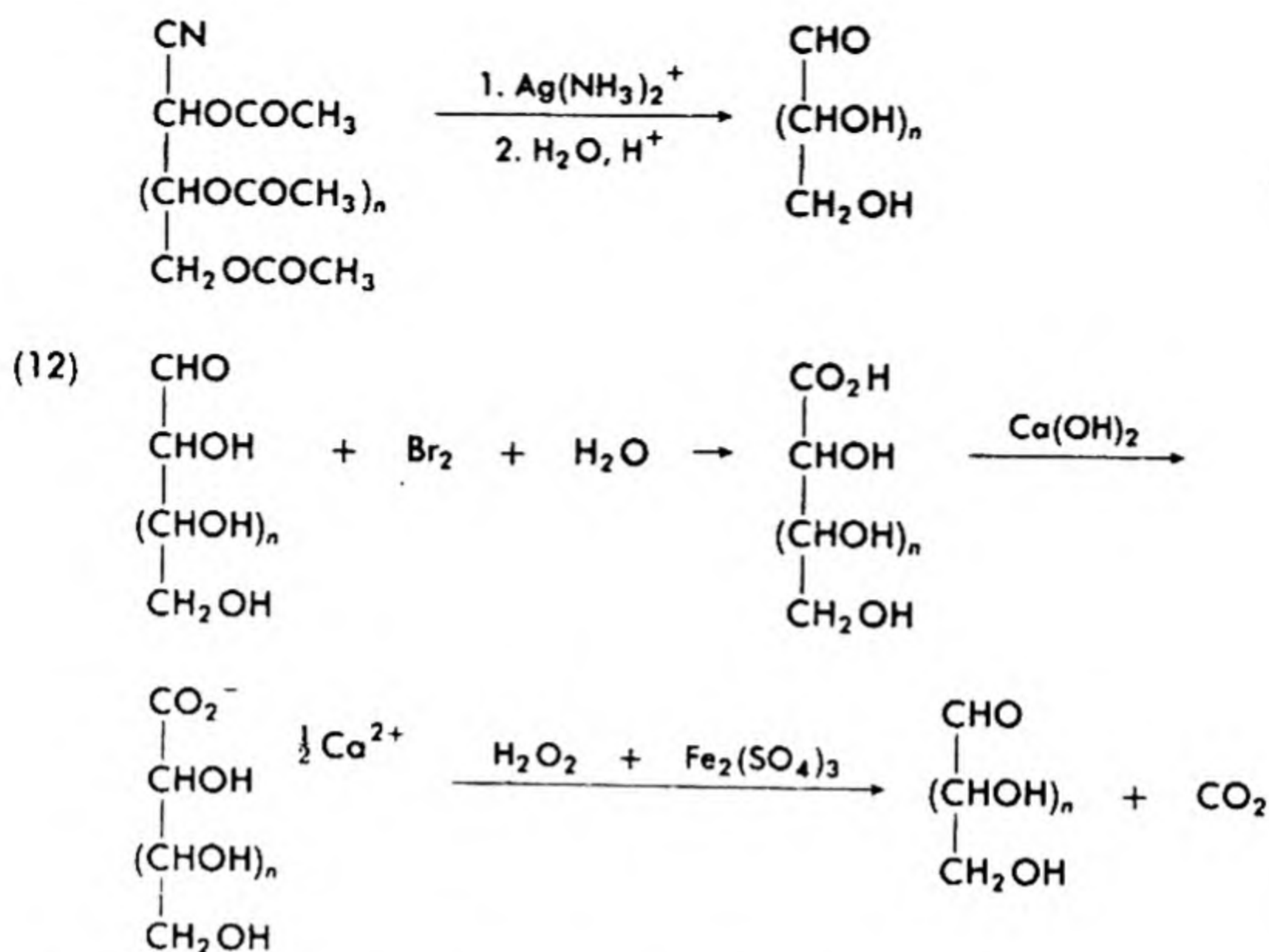


Vigorous reduction of the seven-carbon lactone (I) with hydriodic acid results in the formation of heptanoic acid (eq. 10). This demonstrates the straight-chain nature of the carbon skeleton of glucose, as well as its aldehyde (as opposed to keto) structure.



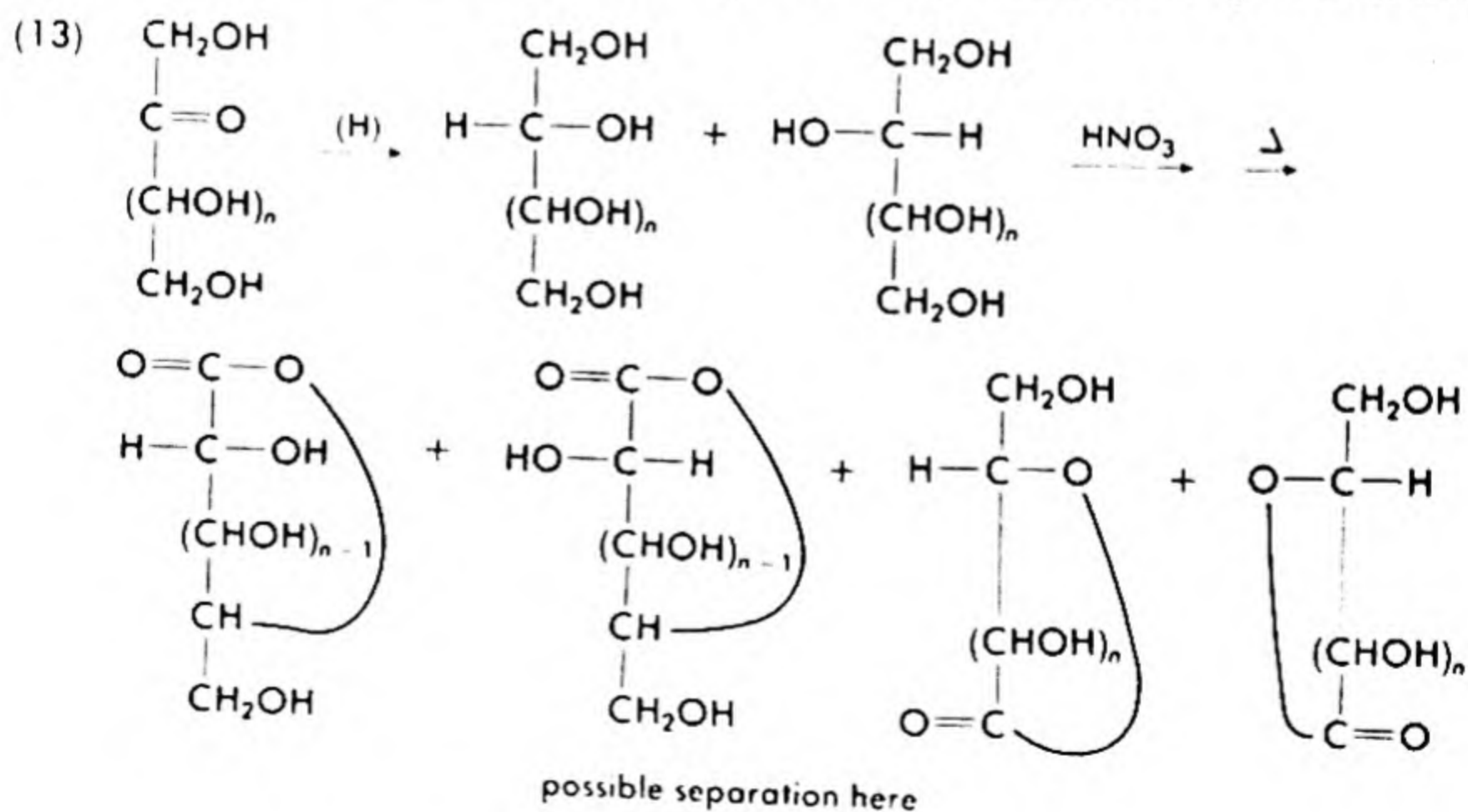
Degradation of aldoses to aldoses with one less carbon atom can be accomplished by either of two methods. In one, the *Wohl degradation*, the aldose is treated, in effect, in retrograde order of the Kiliani synthesis. The method is summarized in outline (11). The second method is the *Ruff degradation* (outline 12).

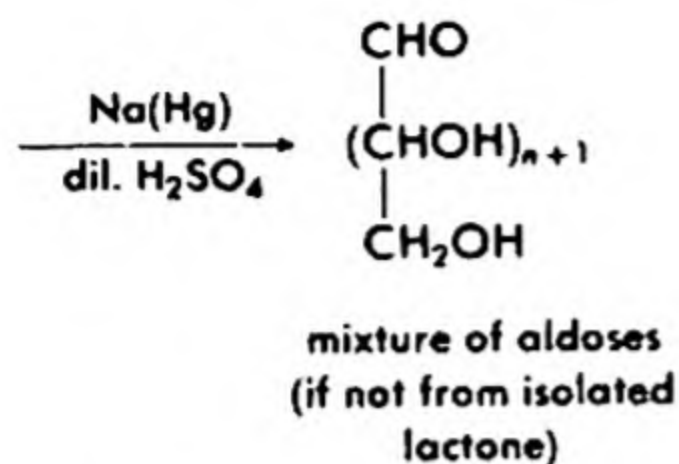




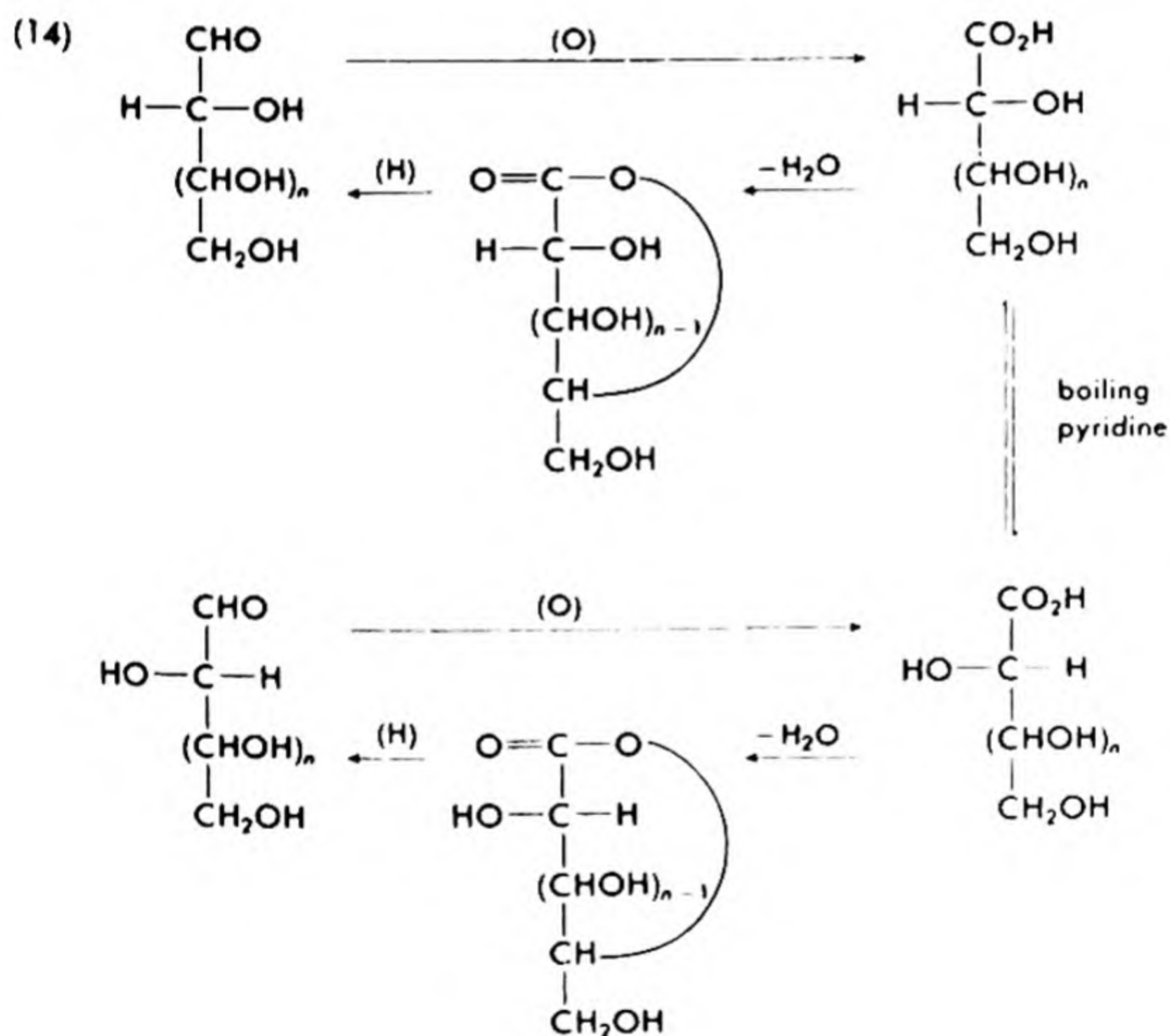
Conversion of an aldose to a 2-ketose involves formation of the 1,2-dicarbonyl compound, either by osazone synthesis and hydrolysis or by oxidation of the 2-hydroxy group with hydrogen peroxide and ferric sulfate. The aldehyde group can be reduced preferentially with powdered zinc and acetic acid.

The reverse, conversion of a ketose to an aldose, is more equivocal. The first step is reduction of the ketose to the two corresponding stereoisomeric polyols. Either of the two primary alcohol groups of a molecule of each polyol is then oxidized to yield a lactone mixture. The lactones are then reduced to aldoses. Either the mixture of intermediate lactones or that of final aldoses must be separated by fractional crystallization.



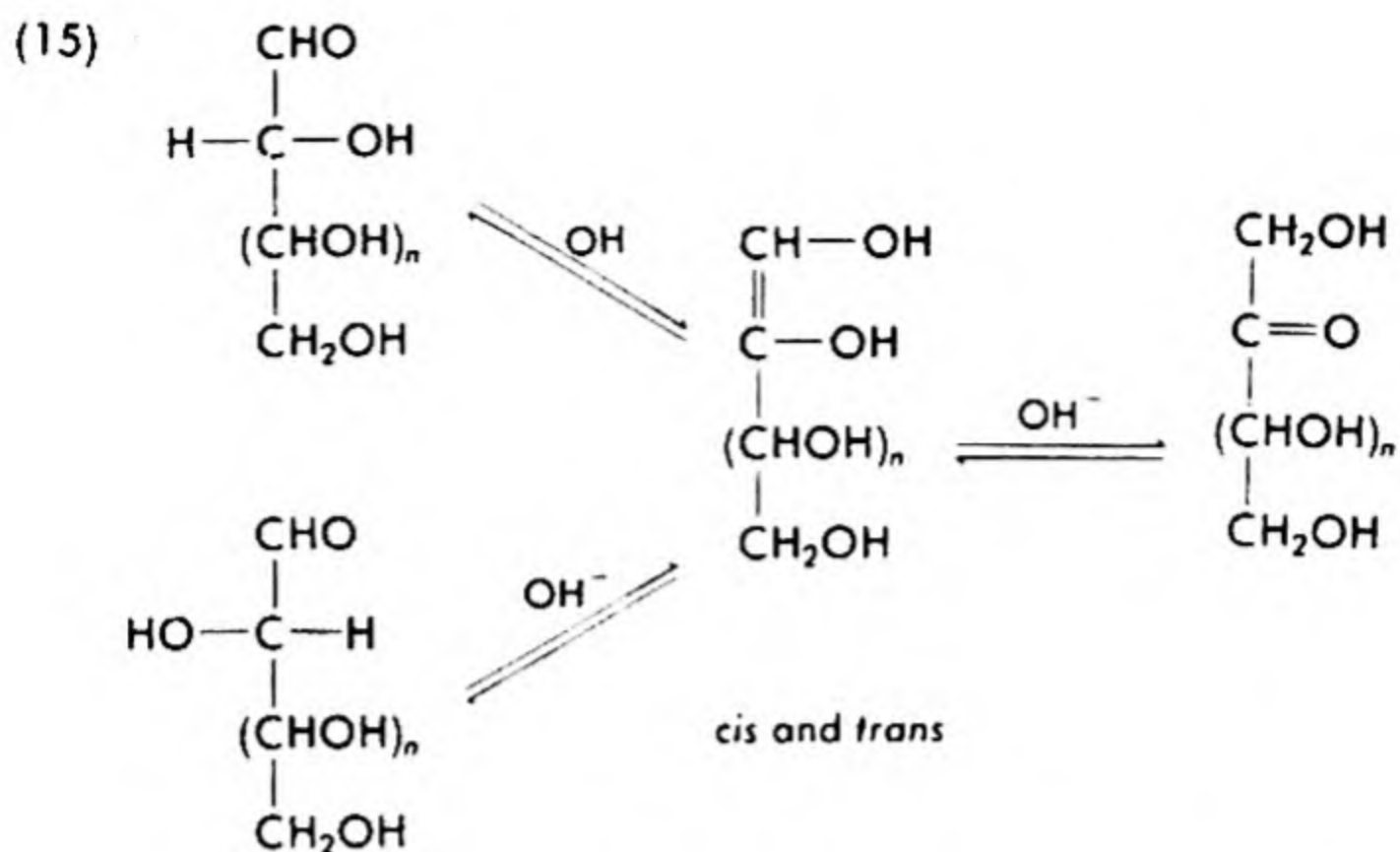


Conversion of an aldose to its epimer at C_2 is readily accomplished. In practice, epimerization depends upon formation of an equilibrium between the two epimeric aldonic acids in boiling pyridine. Consequently, the same equilibrium results by starting with either epimer (see outline 14).

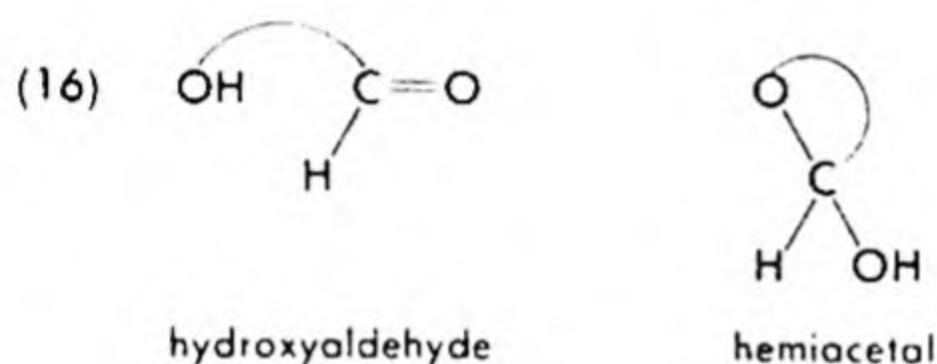


Another method of epimerization introduces the ketose into the equilibrium. Treatment with dilute alkali operates through enediol forms to give the equilibrium mixture shown in outline (15).

(5) *Further Structural Details of the Glucose Molecule.* The data given thus far are readily accommodated by the idea that glucose is a mixture of tautomers involving equilibrium between free hydroxyaldehyde (2,3,4,5,6-pentahydroxyhexanal) and one or more internal hemiacetal forms (eq.

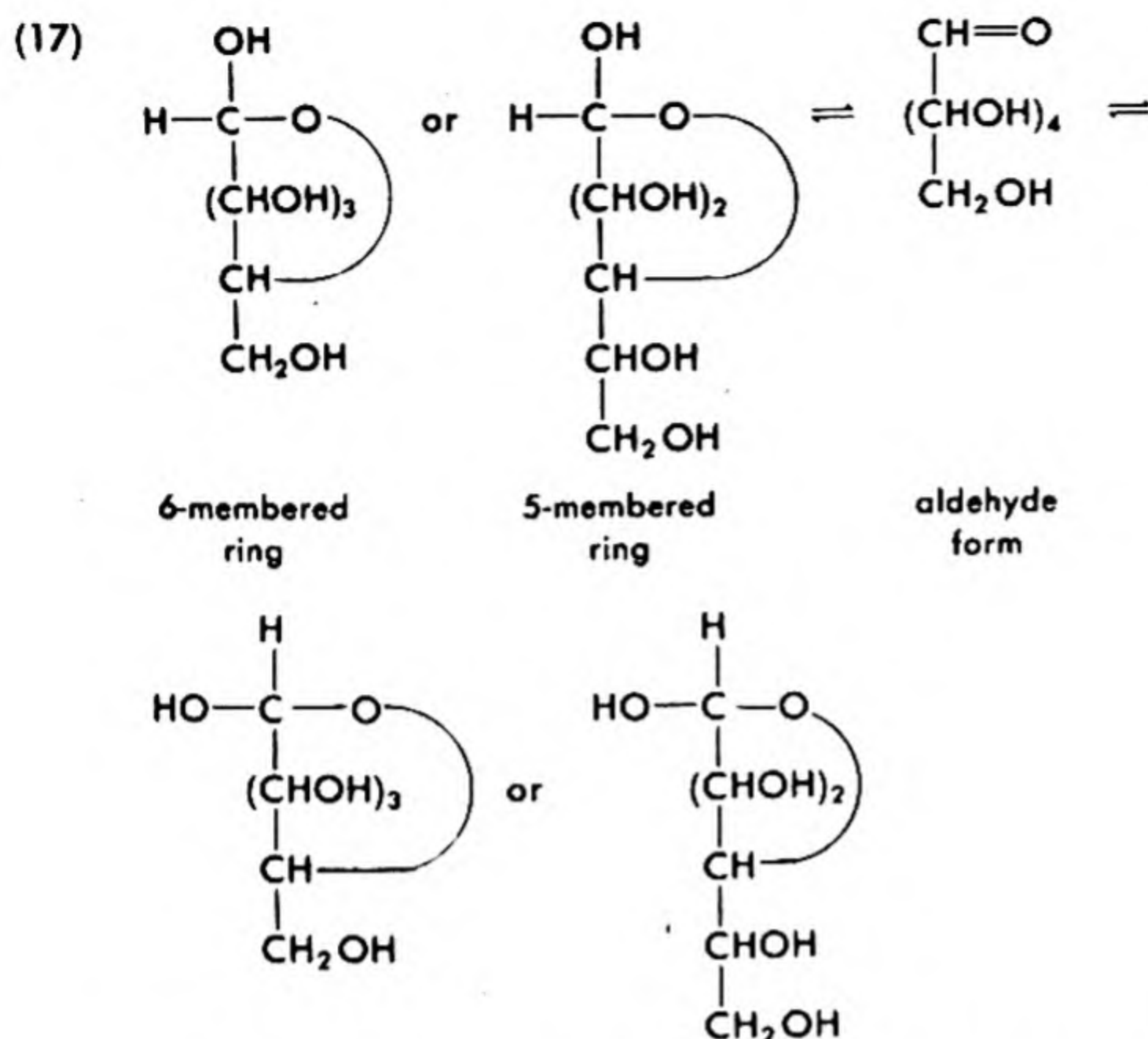


16). Thus certain reactions already described are those of aldehydes, while the formation of an acetal (eq. 2) is that of a hemiacetal.

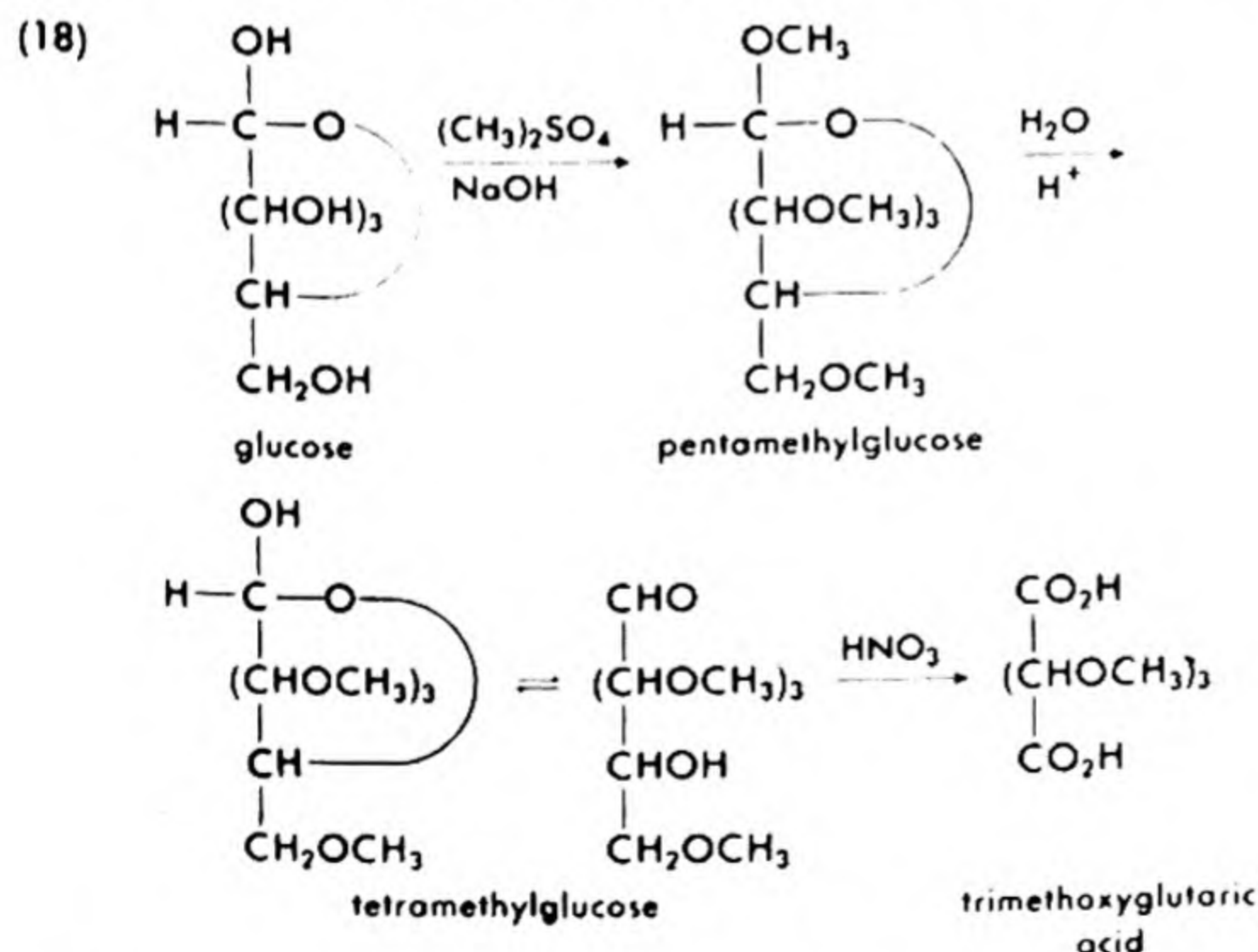


Although there must be small amounts of free aldehyde form present, the principal substances in a solution of glucose are the hemiacetals, and we must now inquire into their number and their structures. Experimentally, two hemiacetals, α and β , termed anomers, are obtainable by special procedures. Thus, when glucose is crystallized from solution at room temperature, the α anomer is obtained. It has a specific rotation, $[\alpha]_D = +111^\circ$ when initially dissolved in water, but the rotation gradually falls to $[\alpha]_D = +52.5^\circ$. Crystallization of glucose at about 100° results in the β anomer, $[\alpha]_D = +19^\circ$. The rotation of the solution of the β anomer gradually increases to $[\alpha]_D = +52.5^\circ$. This change in rotation with time, which is catalyzed by both acids and bases, is called *mutarotation* and is caused by conversion of either anomer to an equilibrium mixture of the two containing 63% of β and 37% of α anomer.

The mutarotation of glucose and the existence of two crystalline forms are accountable on the basis of the formation of cyclic hemiacetals (outline 17) with introduction of an additional asymmetric center at carbon 1. We have noted many times before that both five- and six-membered rings are readily formed, and therefore sugar chemists had to undertake a study of the ring size in sugars. W. N. Haworth shared the 1937 Nobel prize for work in this area.

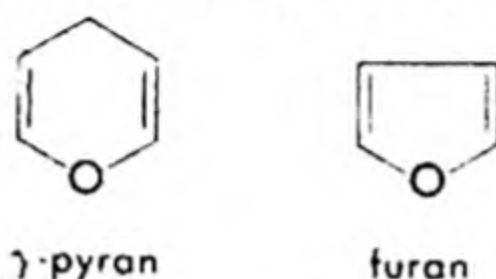


To ascertain the structure of the cyclic form of glucose, the molecular configuration must be secured so that the molecule cannot change structure during a chemical reaction utilized for analysis. This apparently is achieved¹ by complete methylation of glucose with methyl sulfate and



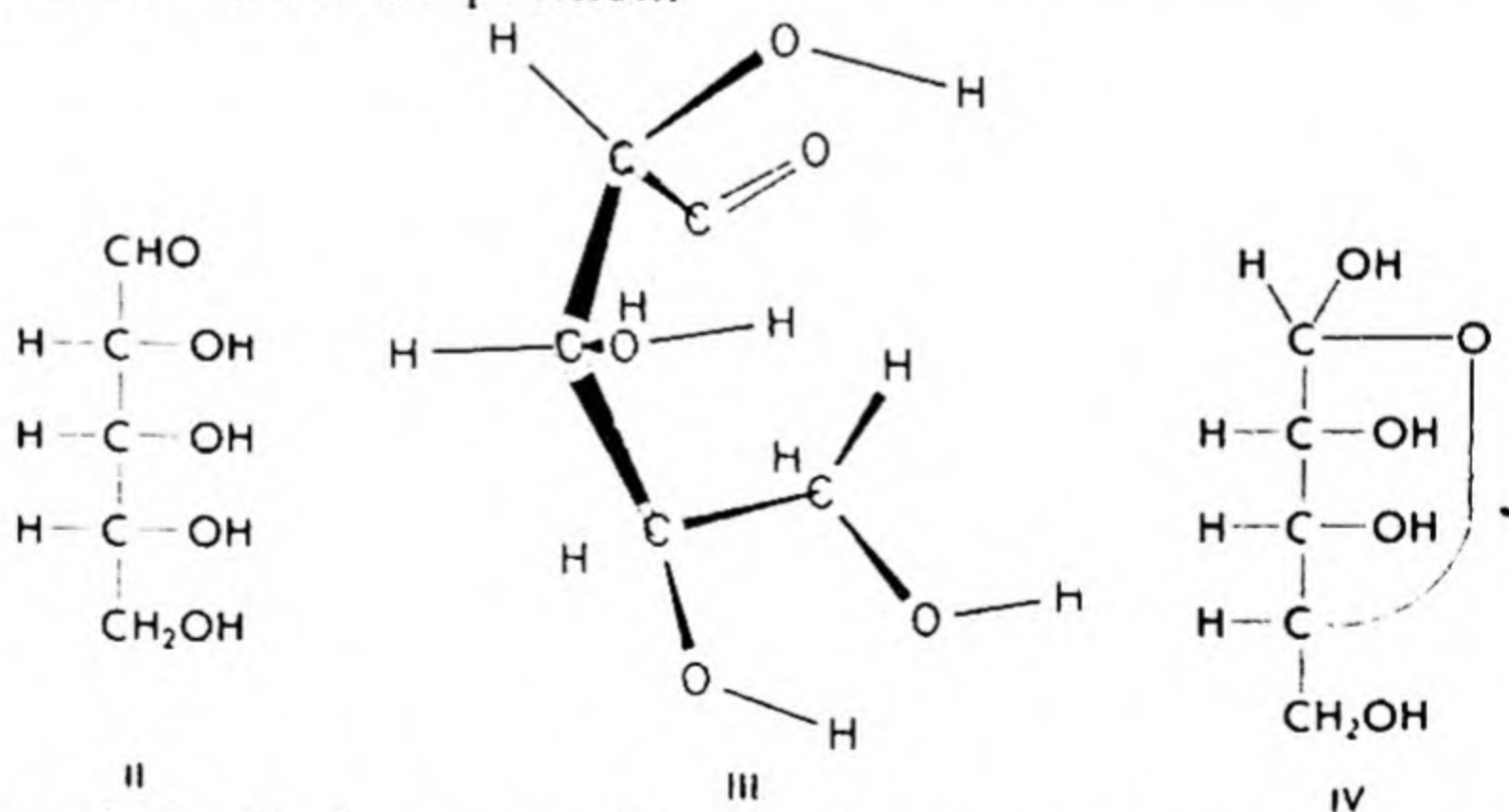
¹ The assumption is made that the reagent reacts more or less equally rapidly with all of the equilibrium species, and thus does not appreciably affect the analysis.

sodium hydroxide. Hydrolysis of pentamethylglucose in acid then frees the aldehyde group and also the hydroxy group involved in the acetal linkage. Oxidation of the tetramethylglucose occurs at the aldehyde group and the free hydroxy group. Upon oxidation the tetramethylglucose forms a trimethoxyglutaric acid. These reactions are summarized in outline (18). Those sugars or sugar derivatives having a five-membered ring lead to dimethoxysuccinic acids by the Haworth procedure. Since the six-membered ring is structurally related to pyran, a six-membered acetal ring in a sugar is called a *pyranose ring*. A five-membered ring is called a *furanose ring* because of its relationship to furan.



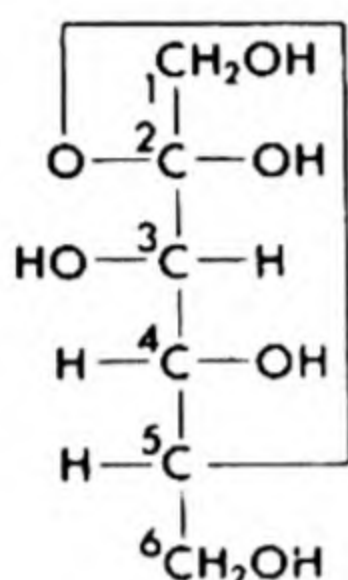
Structural analysis of the other aldoses and the ketoses follows a pattern much like that outlined for glucose.

(6) *Cyclic Formulas for Monosaccharides*. After his monumental work determining the relative configurations of the aldohexoses and aldopentoses (described in the next section), Emil Fischer devised a projection formulation to represent the open (aldehydo) forms of these monosaccharides. In the Fischer projection, the carbon chain is represented vertically and the bonds from each carbon atom to its neighboring carbon atoms are thought of as lying behind the carbon atom under consideration. The hydrogen atoms and hydroxy groups are considered to project up in front of the carbon atom to which they are attached. Thus, the configurational formula, II, represents a molecule in which all hydroxy groups are on the right side and all hydrogen atoms on the left side and the middle of the carbon chain loops up toward the observer, III. The top carbon atom is the 1-position.

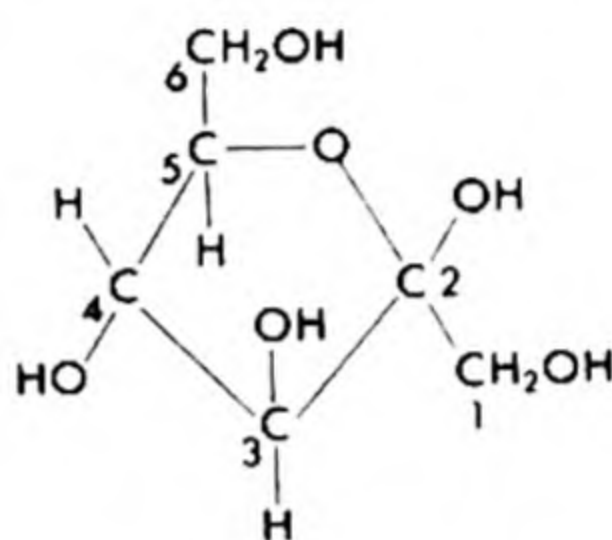


Although the Fischer projection serves well enough for the open forms of the monosaccharides, it is awkward when used to represent cyclic

forms, such as IV. The long, bent "bond" between the oxygen atom and one of the carbon atoms does not represent the situation well; hence its use is misleading in a formula purporting to be a spatial representation of a molecule. To correct this, Haworth devised modified projection formulas which represent carbohydrates in conventionalized cyclic forms. The ring oxygen is usually placed at the upper right, with the carbon atoms placed in clockwise order of numbering after the oxygen atom. Hydroxy groups placed to the right in Fischer projections point downward in Haworth projections; those to the left in Fischer projections point upward in Haworth projections. Formulas below show Fischer and Haworth projections of α -D-fructofuranose and of the anomeric β -D-fructofuranose.

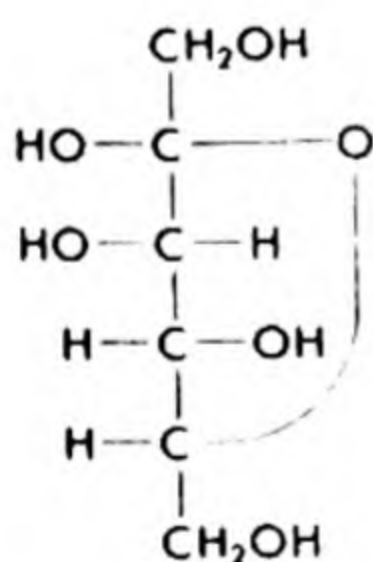


Fischer
projection

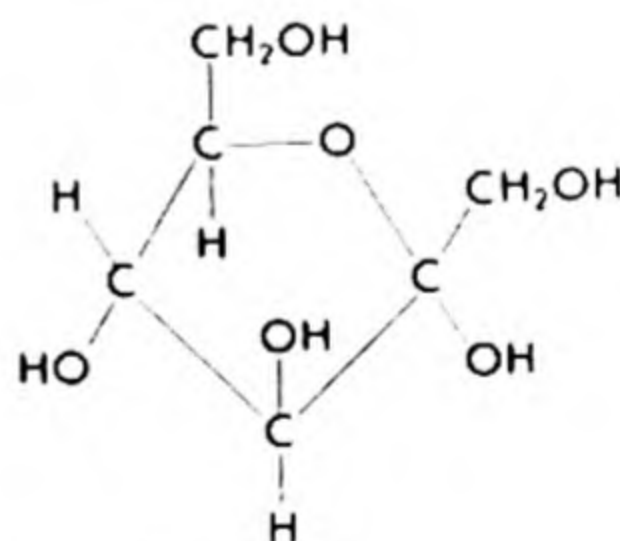


α -D-fructofuranose

Haworth
projection



Fischer
projection

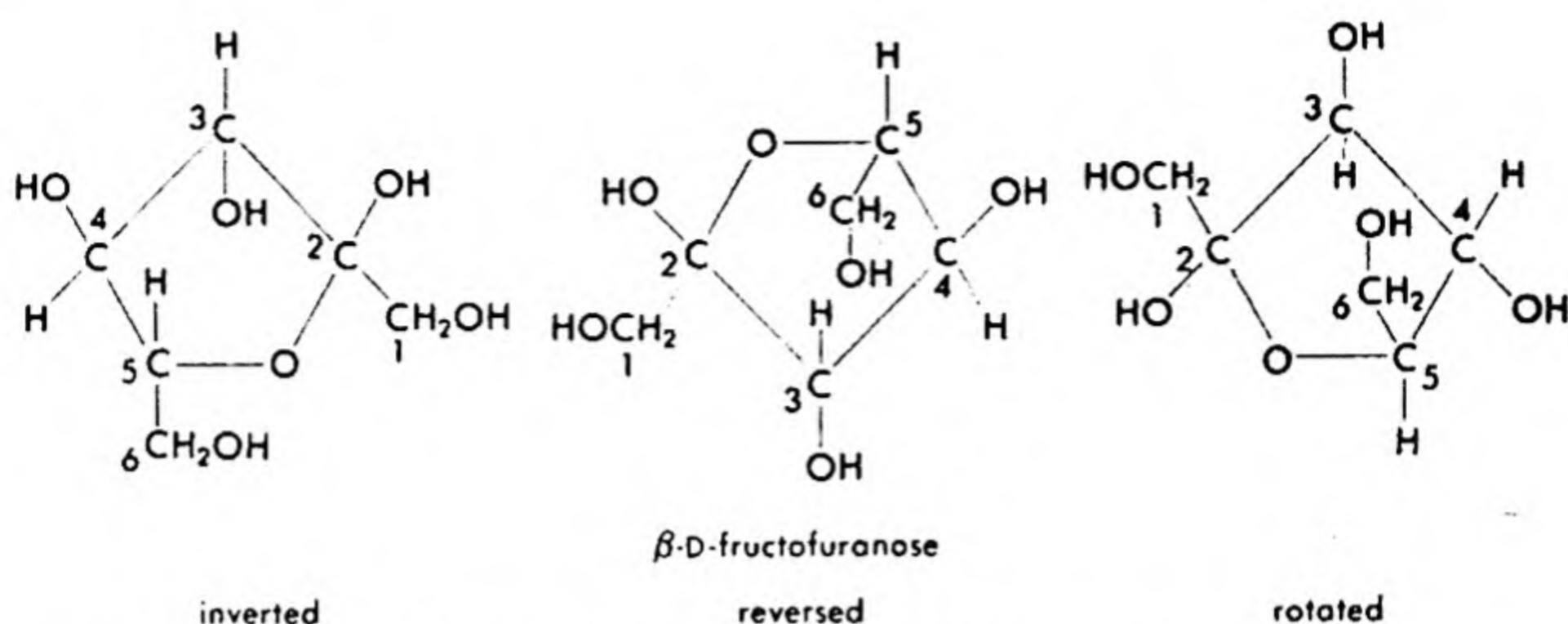


β -D-fructofuranose

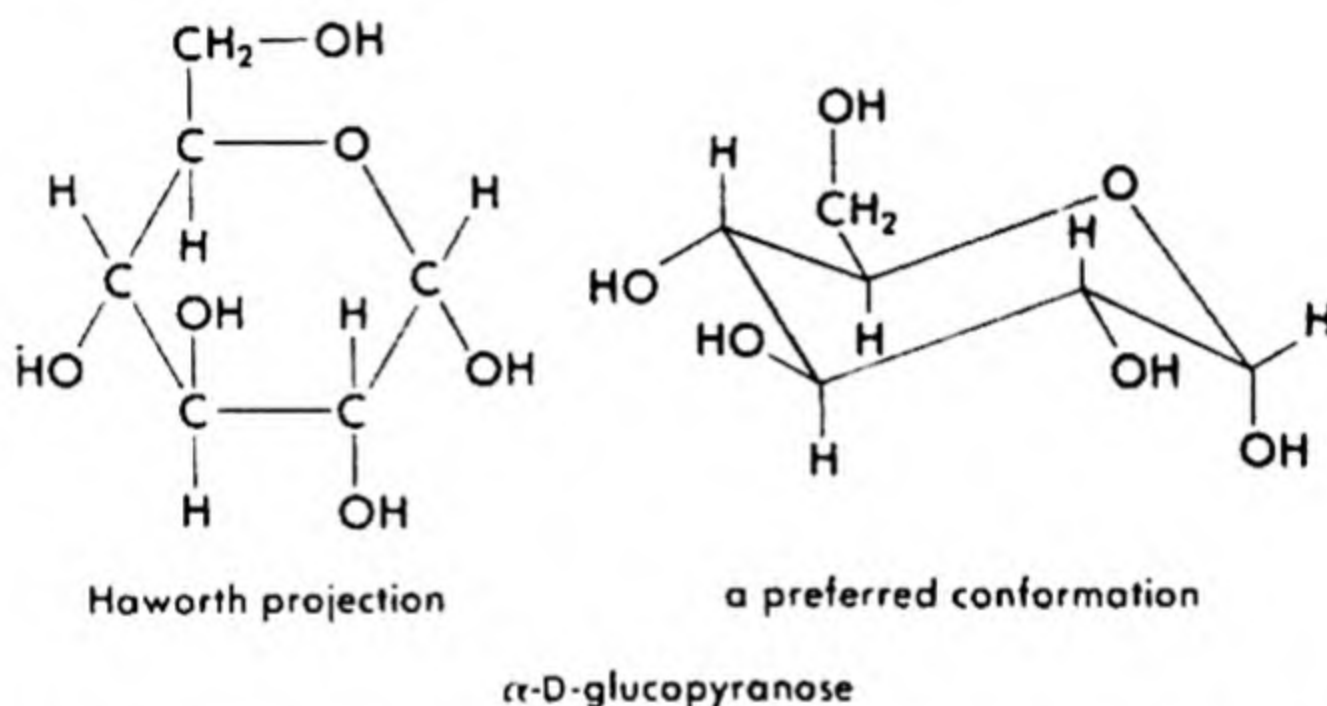
Haworth
projection

In oligosaccharides and polysaccharides the virtues of the Haworth projections are even more striking, since the links between units, as well as the ring oxygens, must be distorted in Fischer projections, whereas Haworth projections cope well with this feature.

Sometimes the Haworth projection is inverted or reversed so as to avoid other obstacles to clear formulation. The projection is a picture of the ring with the top always farthest from the viewer. Compare the formulas for β -D-fructofuranose below with that given above.



Still more realistic conformational formulas are often used in the consideration of spatial influences on reactivities of equilibrium positions. Compare the Haworth projection of α -D-glucopyranose and the conformational formula below.



(7) *Optical Configurations of Aldoses.* As late as 1885, although the tetrahedral theory of carbon valences required sixteen isomeric aldohexoses and eight aldopentoses, and although several of the required isomers were recognized, the configurations of the monosaccharides remained unknown. It was the great structural chemist, Emil Fischer, who, basing much of his work on studies by Kiliani, Wohl, and Ruff, solved the problem. He required ten years to decipher the relative configurations, but this work served as one of the most elegant examples of the use of classical methods in structural and configurational analysis. For this and for his determination of structures of the purines (cyclic nitrogenous bases), Fischer received the Nobel Prize in 1902.

Fischer's analysis is too involved to give in chronological detail; instead only the general outline of the principles he used is considered.

The point of departure is the establishment of epimeric relationships and relationships among the aldoses via Kiliani's synthesis and the Wohl and Ruff degradations. These relationships are given in Table 38-1. Corresponding to the epimeric and series relationships are the configurational relationships of the aldoses shown in Fig. 38-1. In this figure, the

TABLE 38-1. Kiliani Synthesis Series

Triose	Tetroses	Pentoses	Hexoses
D-Glyceraldehyde	D-threose	D-lyxose	D-galactose
		D-xylose	D-talose
	D-erythrose	D-arabinose	D-idose
			D-gulose
		D-ribose	D-glucose
			D-mannose
			D-allose
			D-altrose

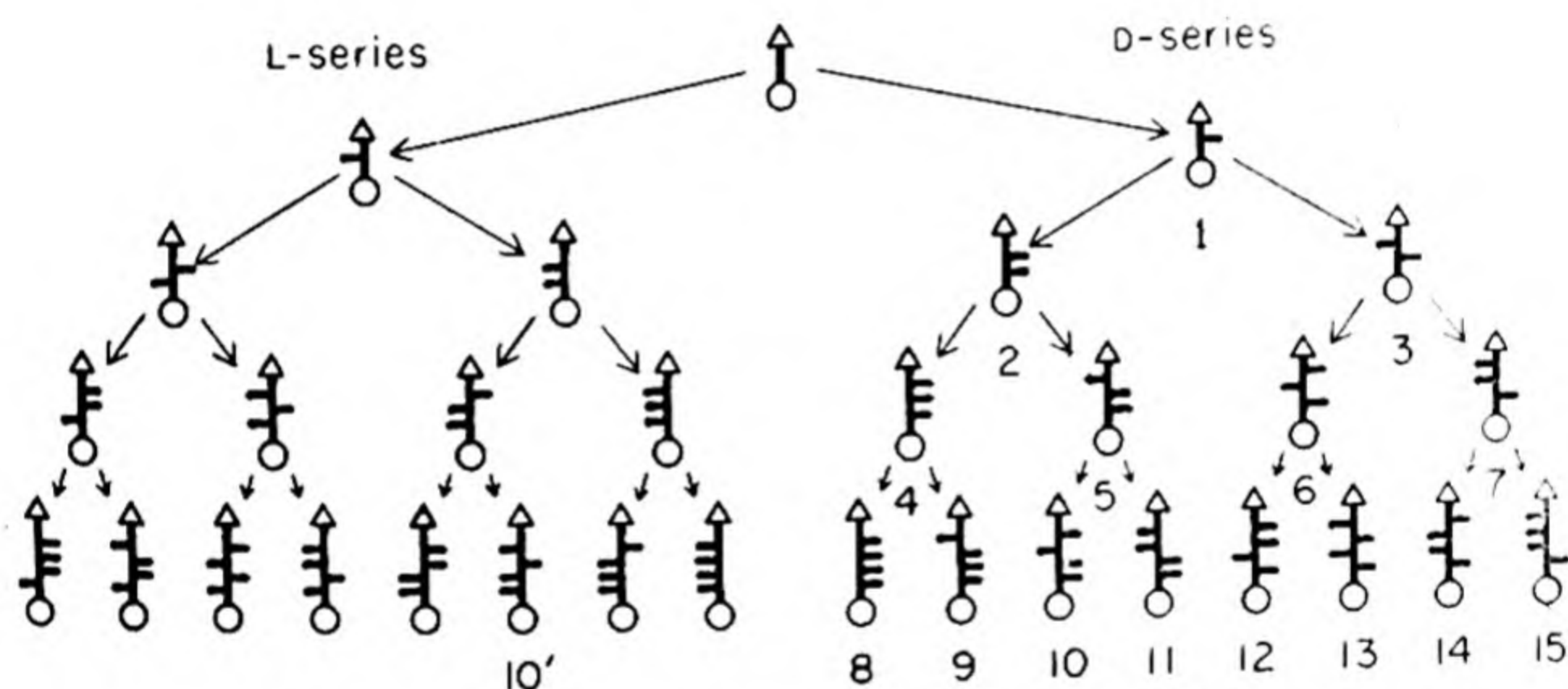
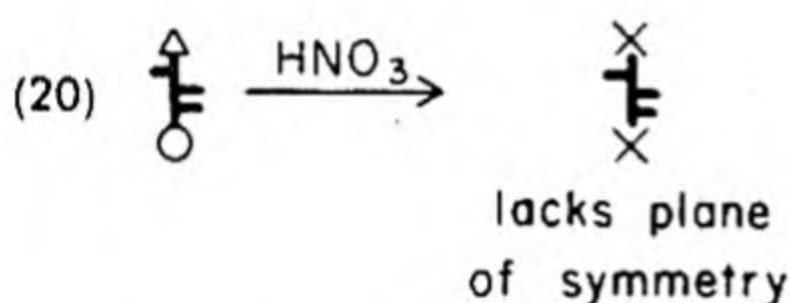
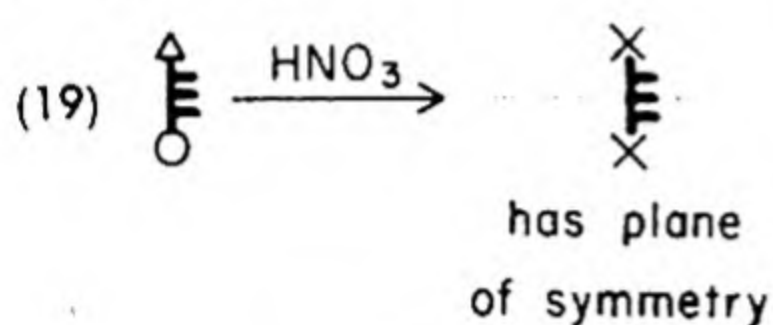


Fig. 38-1. Configurational Relationships of Aldoses.

molecular configurations are indicated by abbreviated Fischer projections, using triangles to represent aldehyde groups, circles to represent primary alcohol groups, and dashes along the chain to represent the orientation of hydroxy groups relative to the backbone of the molecule, which is the vertical line connecting the circle and triangle. Since the optically opposite series of enantiomorphs bear exactly the same relationships within a series, but in mirror image position, the configurational relationships of only one series need be considered. The D-series aldoses are those discussed in the analysis. These are the aldoses that can be built up from D-glyceraldehyde by successive Kiliani syntheses and, therefore, have the lowest asymmetric carbon in the Fischer convention attached to hydroxy on the right, hydrogen on the left.

It should be apparent at first glance that whereas D-glyceraldehyde can be assigned by convention the configuration 1 in Fig. 38-1, the relation-

ships between the other numbered formulas and the aldoses listed in Table 38-1 are by no means self-evident. Tetrose 2 might be either D-threose or D-erythrose. To ascertain the configurational identity of the various aldoses, Fischer resorted to oxidations leading to glycaric (saccharic) acids. These yield structurally symmetrical compounds, of which a certain number should be meso acids. For example, oxidation of ribose and xylose by nitric acid yields optically inactive acids; hence, these two aldopentoses must be 4 and 6 (not necessarily in this order). To check this, the carboxyl groups can be indicated by another sign, like X, and the configuration of the molecule checked for a plane of symmetry (outlines 19 and 20).



Lyxose and arabinose, which yield optically active glycaric acids, are 5 and 7 (not necessarily in this order). Talose and galactose are epimers derivable from lyxose; glucose and mannose, epimers derivable from arabinose. Of these hexoses, only galactose yields a *meso* glycaric acid; hence galactose is 14 and talose 15. Lyxose must be 7; arabinose, 5. Xylose, the epimer of lyxose, is 6, and ribose, the epimer of arabinose, is 4. Another inactive acid is produced by allose. Hence, allose is 8. Altrose, which yields an optically active acid and is the epimer of allose, is 9.

To establish the configuration of glucose, recourse was made to Kiliani syntheses to the aldoheptoses. Oxidation of the two aldoheptoses yields one optically active glycaric acid and one *meso* acid. Consideration of formulas 10 and 11, the epimeric hexoses related to arabinose, shows that the substance which produces this result must have the configuration 10. (The student should write out and check this for himself.) Hence, glucose has the configuration 10. Mannose, the epimer of glucose, which yields two optically active heptoglycaric acids, is 11.

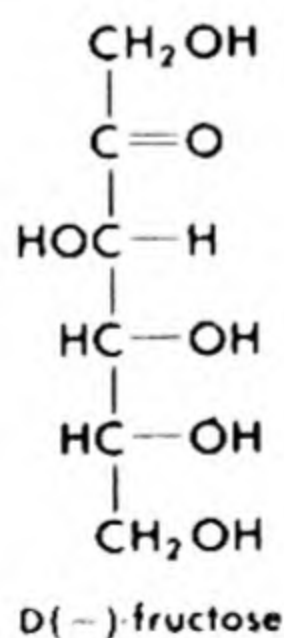
Upon oxidation, glucose gives the glycaric acid specifically named D-saccharic acid. Gulose yields the enantiomorph, L-saccharic acid. Since D-gulose cannot belong to the L-series, this means that when the aldehyde group and the primary alcohol group lose their identity by transformation to carboxyl groups, the same result ensues as when L-glucose is oxidized. To see the relationship, one rotates a model of gulose 180° so that

its aldehyde group coincides with the primary alcohol group of L-glucose, 10', and its primary alcohol group coincides with the aldehyde group of L-glucose. The formula which fits this description is 12. The remaining hexose, idose, is 13.

Occasionally, one wishes to indicate the direction of optional rotation of an optically active material. This is done by placing (+) or (−) between the series indication and the remainder of the name. Thus, D(+)-glucose, D(−)-ribose, D(+)-glyceraldehyde, and D(−)-tartaric acid are examples.

(3) *Importance of Monosaccharides.* D-Glucose occupies a pre-eminent position in biochemical reactions and in occurrence in nature, although many of its naturally occurring derivatives have furanoside cyclic structure rather than pyranose rings. Its manufacture in plants by photosynthesis provides an energy store for all members of both plant and animal kingdoms. Glucose is also the monomeric unit for cellulose, the structural framework in woody plants. In combination as glucosides, which are acetals formed with alcohols, phenols, and related compounds, glucose is present in many types of functional, regulatory, and protective materials in plants. Glucose is the sugar found in blood in the largest amount. Its importance to life is indicated in the fact that no glucose is excreted until a certain threshold concentration is exceeded, as in diabetes, whereupon glucose is found in the urine. Other names for glucose are dextrose (from its optical rotation) and grape sugar.

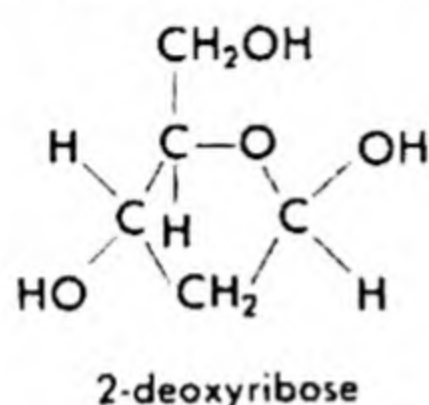
Fructose, a ketose, forms the same osazone as glucose. Hence, the configurations of hydroxy groups on carbon atoms 3 through 5 are the same as those on the corresponding positions of glucose. Since fructose



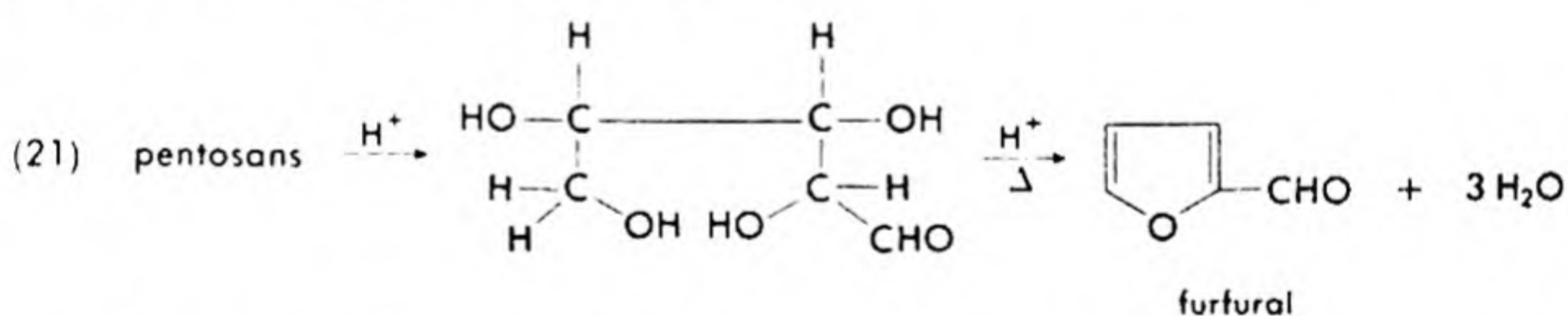
has no other asymmetric centers, this effectively establishes its configuration. Fructose is the sweetest known sugar. It is also called levulose (due to its levorotation of plane-polarized light). The anomeric form of fructose usually isolated is β -D-fructose, $[\alpha]_D = -133.5^\circ$. The equilibrium rotation is $[\alpha]_D = -88.5^\circ$.

Ribose is an important pentose which, although not free in nature, can

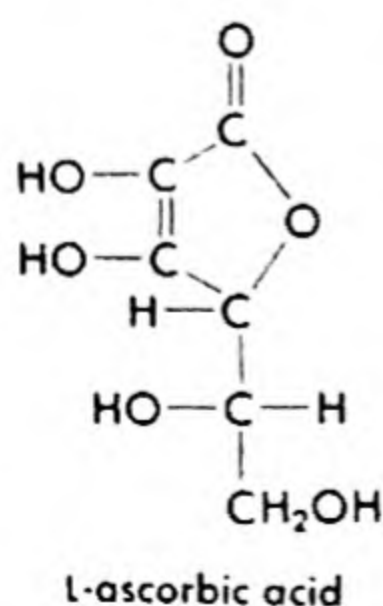
be isolated from a variety of biologically active substances. D-Ribose units are present in vitamin B₁₂, in cellular material called ribonucleic acid, RNA, and in several enzymes related to these materials. One type of RNA contains the code for specific protein synthesis. In riboflavin (vitamin B₂), the related alcohol, ribitol, is a structural unit. Ribulose, a ketopentose, is related to ribose in the same way fructose is related to glucose. Ribulose and ribose participate in the photosynthesis cycle of carbohydrates. 2-Deoxyribose (2-deoxy means that the oxygen at C₂ is missing) is a constituent in deoxyribonucleic acids, DNA, which carry the genetic code.



Xylose and other pentoses occur in polymeric material called hemicelluloses or pentosans, which are constituents in the woody parts of all plants. Pentosans obtained from corn cobs or oat hulls are converted industrially in large quantities into furfural (eq. 21) by the action of mineral acid on pentosan-containing materials. The product is isolated by steam distillation from the remaining decomposition products. Furfural is used as a solvent and is an intermediate in the synthesis of a variety of compounds containing the furan ring.



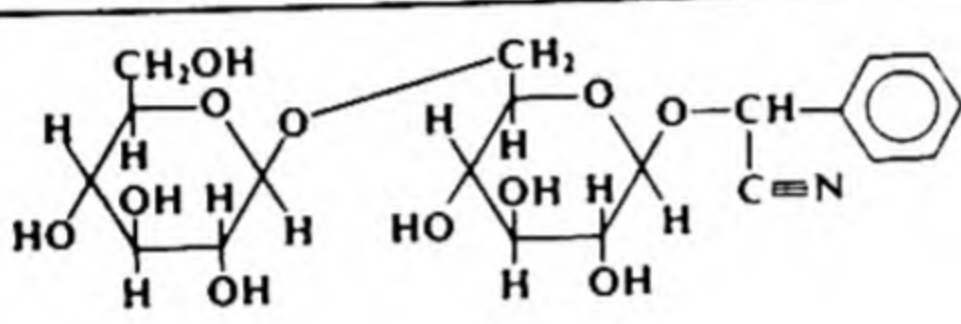
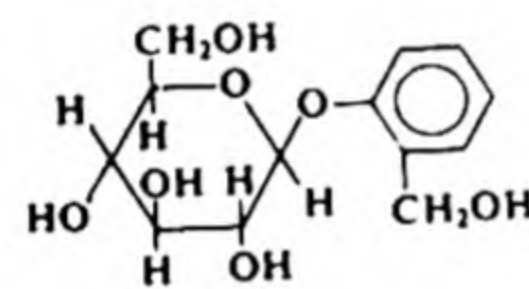
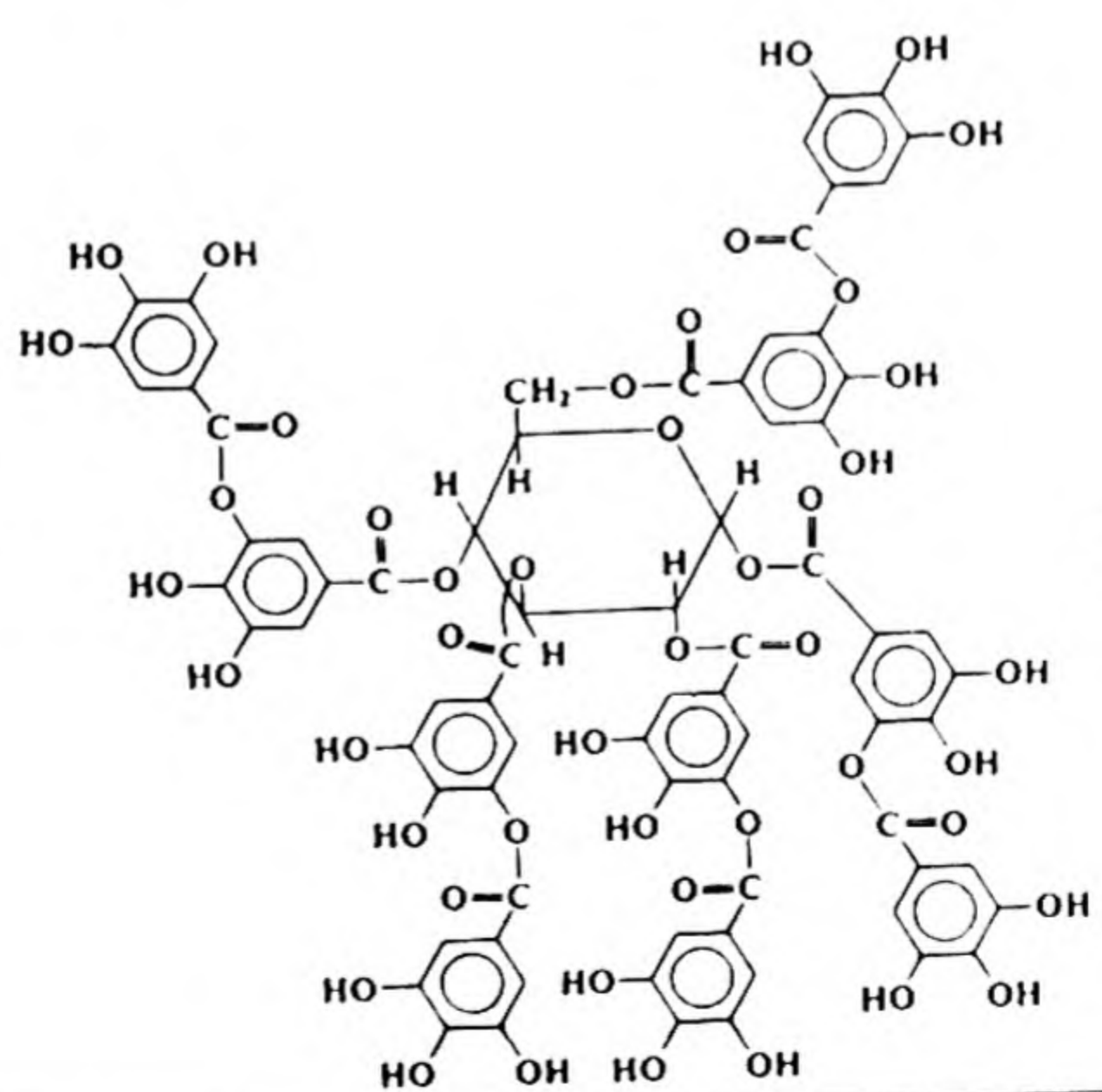
L-Ascorbic acid (vitamin C) is the enol form of the ketolactone related to L-galactose or L-talose. The acidity of this compound is due to the enol groups, of which the hydroxy on C₃ is stronger due to conjugation with the carbonyl group at C₁.



C. Glycosides

Carbohydrate derivatives in which the carbonyl group has formed an acetal (or ketal) linkage, as in 1-methylglucose, are called glycosides. The portion of a glycoside that is attached by an acetal linkage to a carbohydrate and is noncarbohydrate in nature is called an *aglycone*. Also classed as glycosides are certain esters in which the hemiacetal hydroxy group is acylated. A vast number of important medicinal drugs, flavoring agents, and natural dyes are found in their plant sources as glycosides. A few glycosides and their structures are given in Table 38-2. The structures have been determined by hydrolysis to the carbohydrates and the agly-

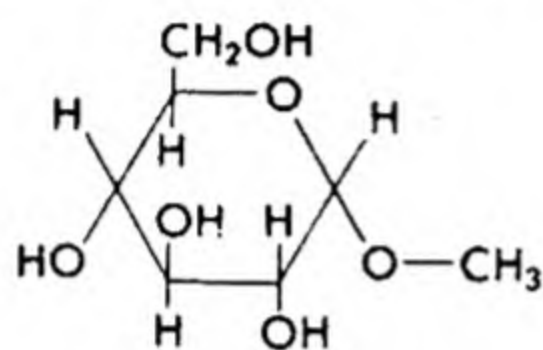
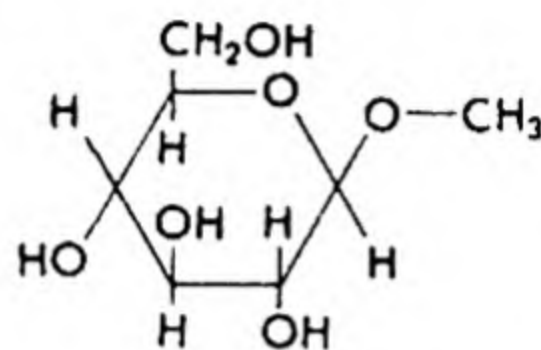
TABLE 38-2. Some Naturally Occurring Glycosides

Name	Formula	Source
Amygdalin		Seeds of peaches, plums, bitter almonds
Salicin		Willow bark
Tannic Acid (One of several tannins. Used in leather tanning and as mordant for basic dyes)		Tree barks (tan oak, quebracho)

cones and by the usual methods of determination of position of substitution.

The sugar units in oligosaccharides and polysaccharides are linked together with glycosidic linkages.

Simple glycosides are usually named, like 1-methylglucose, by designating the alcohol radical, position of attachment, and the sugar. Since the replacement of hydrogen by a nonlabile group fixes the molecule in a definite configuration about the anomeric carbon atom, two optical isomers are obtainable, designated by the Greek letters α , with the aglycone *trans* to C_6 , and β , with the aglycone *cis* to C_6 .

methyl α -glucosidemethyl β -glucoside

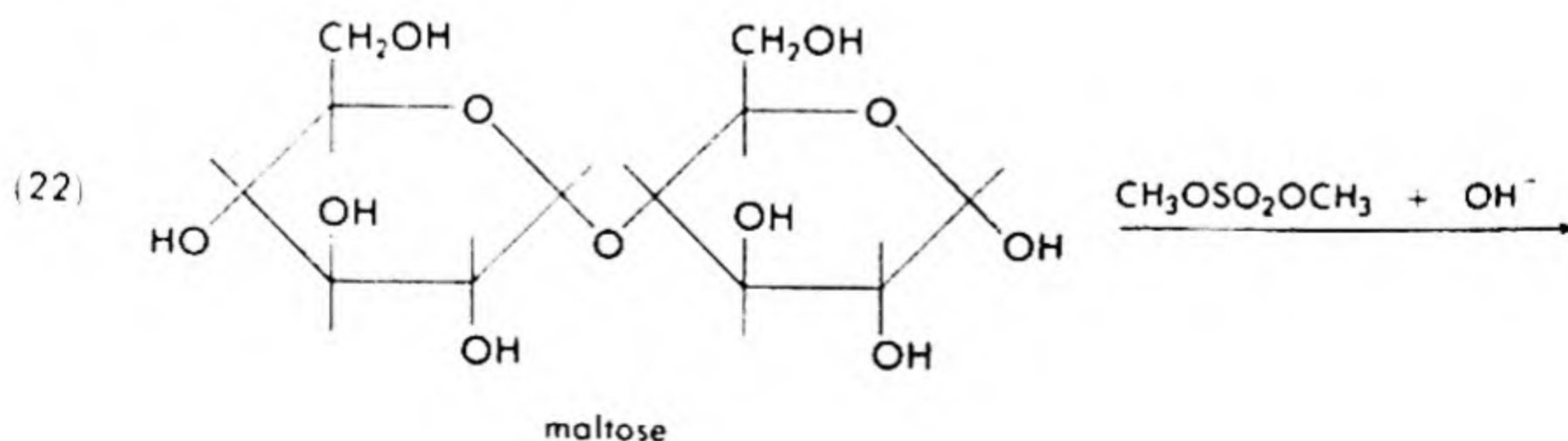
Systematic nomenclature of glycosides is better illustrated than explained. Rules for nomenclature of these and other carbohydrate derivatives are given in "Rules for Carbohydrate Nomenclature," ACS Official Report, *Chem. Eng. News* **31**, No. 17, 1776-1783 (April 27, 1953).

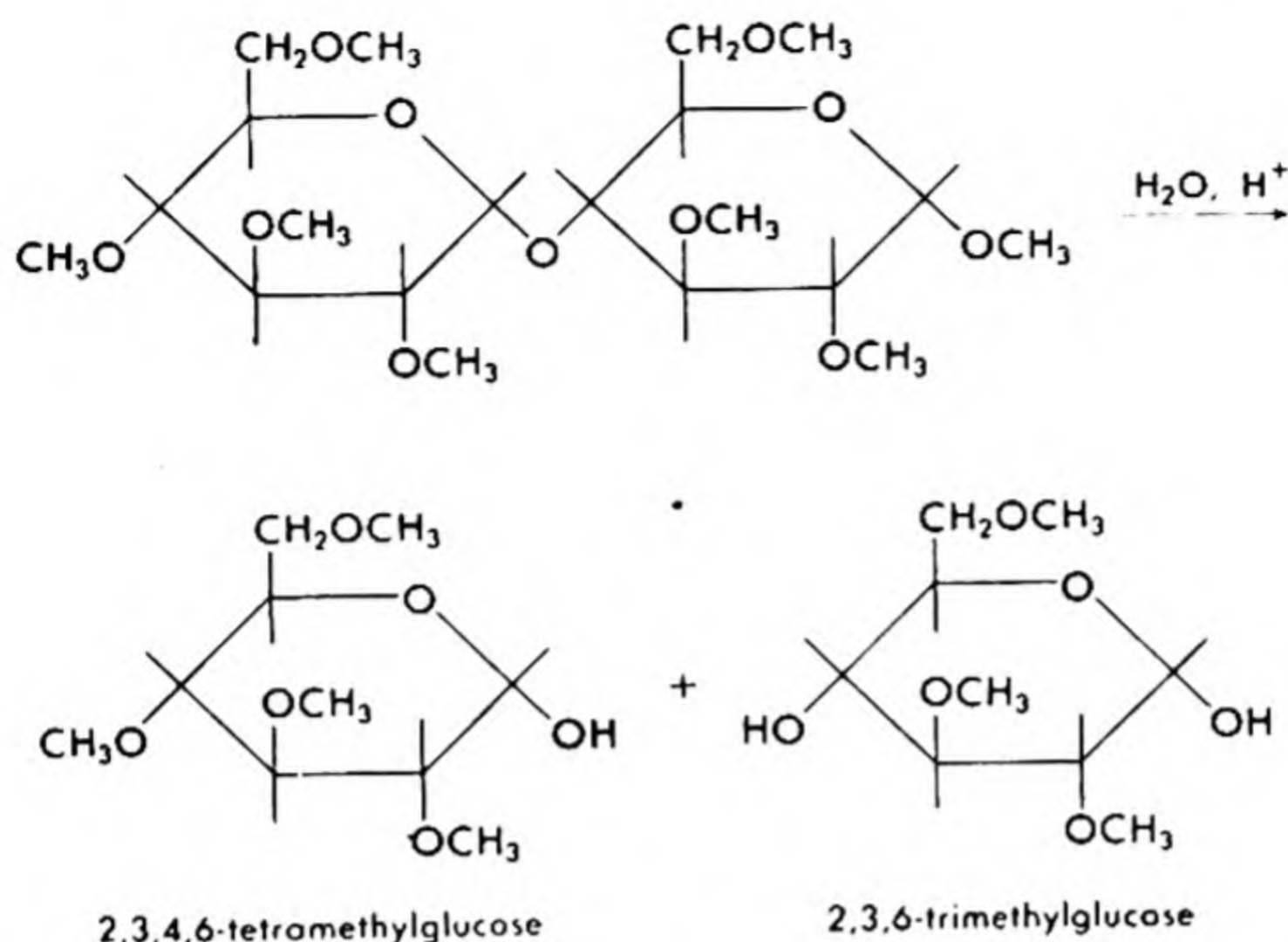
D. Disaccharides

(1) *Physical Properties.* Disaccharides are similar in physical properties to monosaccharides, since both have the same kind of polar groups. Like monosaccharides, disaccharides are asymmetric, hence show optical activity.

(2) *Chemical Properties.* Like monosaccharides, disaccharides can be esterified and alkylated.

Hydrolysis of completely methylated disaccharides gives evidence of their ring structures and points of connection. Outline (22) shows the work of Haworth and his associates on maltose. The dilute acid hydrolysis occurs only at acetal links.





The isolated polymethylglucoses were identified as compounds known from earlier studies in which their structures had been elucidated by various degradations. The tetramethylglucose could only have been obtained from the glycosidic sugar unit. The 2,3,6-trimethylglucose was obtained from one unit, which must have been attached by its 4-*O*-position in the glycosidic linkage. This work shows that one of the glucose units in maltose has the hemiacetal structure. As might be anticipated, then, two anomers are isolable. The α anomer has $[\alpha]_D = +168^\circ$; the β anomer has $[\alpha]_D = +118^\circ$, and mutarotation occurs to an equilibrium mixture with $[\alpha]_D = +138.5^\circ$. The presence of the aldehyde form is demonstrated by ready osazone formation and by the reduction of Benedict's and Fehling's solutions. Saccharides of this type are called "reducing sugars."

(3) *Nomenclature.* Because of their length and oral clumsiness, systematic names of disaccharides are seldom used (see §38-1C). Since the systematic nomenclature is closely related to structure and configuration, the names are discussed in the paragraphs devoted to the individual compounds. The main utility of the systematic nomenclature of those oligosaccharides having trivial names is to emphasize structural and configurational relationships.

(4) *Structure of Sucrose.* Hydrolysis of sucrose, $\text{C}_{12}\text{H}_{22}\text{O}_{11}$, by dilute hydrochloric acid or by the enzyme invertase (sucrase) gives an equimolar mixture of glucose and fructose. Since sucrose is not a reducing sugar, the hemiacetal functions of both monosaccharide units must participate in the acetal linkage between them.

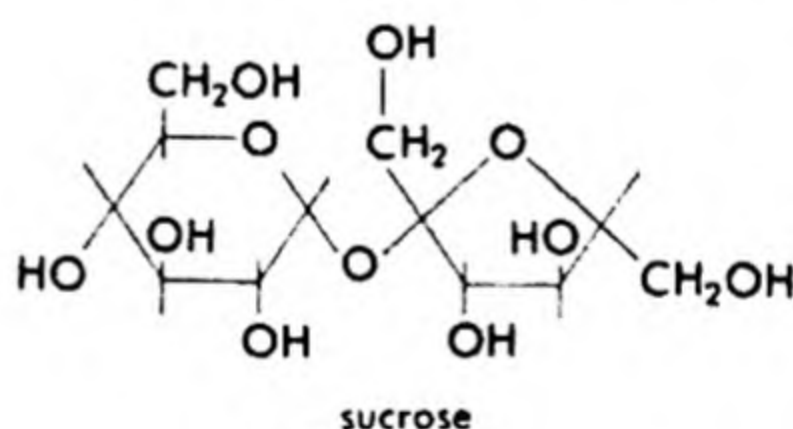
Determination of ring structure is accomplished by complete methylation, hydrolysis, and identification of the separated glucose and fructose

derivatives. Formation of 2,3,4,6-tetramethylglucose shows the glucose unit to have a pyranose ring. Isolation of 1,3,4,6-tetramethylfructose shows the fructose unit to have a furanose ring. Prior knowledge of the stereochemistry of glucose and fructose establishes the relative configuration about seven of the nine asymmetric carbon atoms in sucrose.

Enzymatic hydrolysis rates suggest an *alpha* glycosidic linkage at the glucose unit and a *beta* glycosidic linkage at the fructose unit. Sucrose is named, therefore, α -D-glucopyranosido- β -D-fructofuranoside, or β -D-fructofuranosido- α -D-glucopyranoside. Since both monosaccharide units are glycosidically linked, the order of naming them is indifferent.

As sucrose has no hemiacetal or free aldehyde groups, it does not have anomeric forms, is not a reducing sugar, and does not form an osazone from the intact molecule. The osazone which forms slowly is glucosazone, which arises by acid-catalyzed hydrolysis of sucrose to glucose and fructose, followed by osazone formation.

(5) *Importance of Disaccharides.* Sucrose, also called sugar, cane sugar, and beet sugar (see also the systematic names above), is found universally in the sap and fruit juices of plants. In several, among which the sugar maple, sugar beet, and sugar cane are common examples, the concentration and amount of sucrose available makes possible commercial exploitation. Thus, sucrose is used throughout the world as table sugar. The

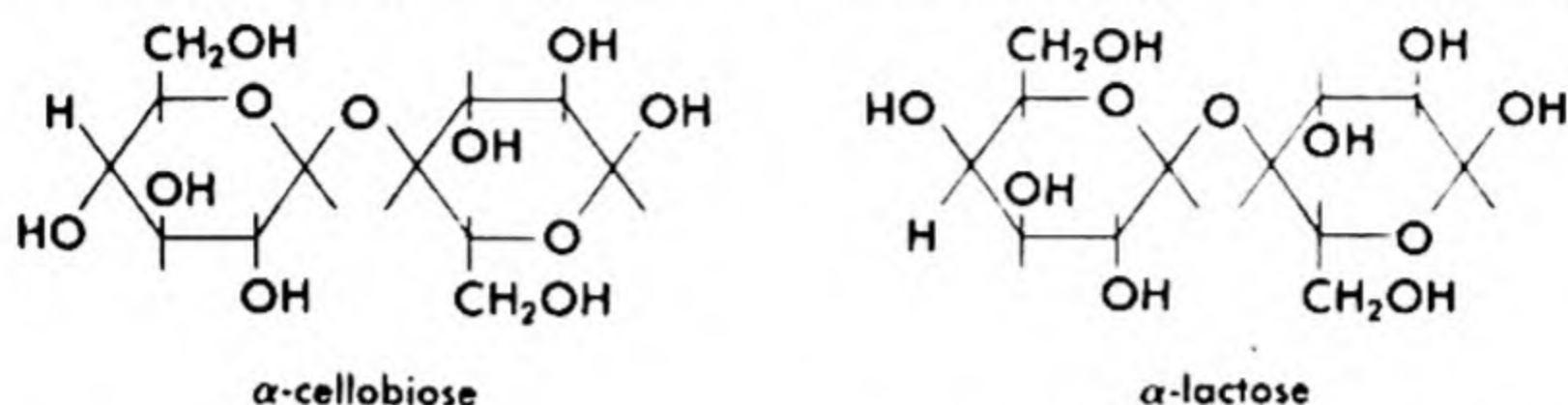


equivalent mixture (honey) of fructose and glucose is considerably sweeter than sucrose (fructose is the sweeter of the two) and industrial users of sugar (e.g., bakers, candy-makers) often hydrolyze sucrose to fructose and glucose before use. The optical rotation of the solution changes from positive to negative during this process, which is thus termed *inversion of sucrose*, and the enzyme used is called invertase.

Maltose is the disaccharide obtained by careful acid hydrolysis of starch, or more satisfactorily, by hydrolysis in the presence of the enzyme diastase. This enzyme is obtained from malt, which consists of young barley sprouts.

Maltose is hydrolyzed by the enzyme maltase (α -glucosidase), which attacks *alpha* glucosides in general. This establishes that the glycosidic bond has the *alpha* configuration. Maltose is thus 4- α -D-glucopyranosido-D-glucose.

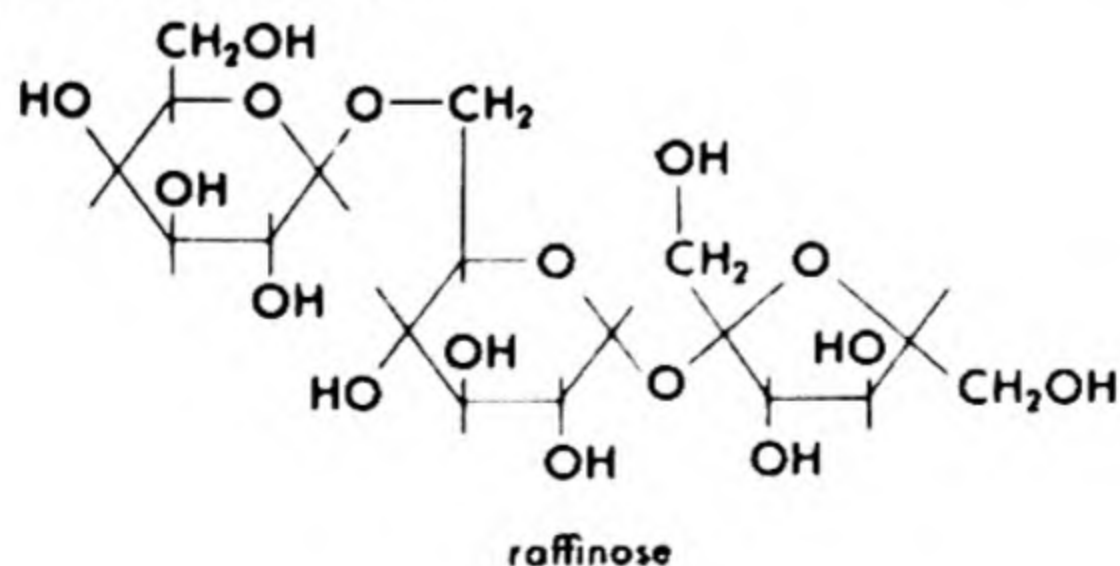
Cellobiose is a disaccharide obtained by very careful hydrolysis of cellulose. Cellobiose differs from maltose only in that the glycosidic linkage is *beta*. This is established by failure of maltase to hydrolyze cellobiose and by efficacy of emulsin (β -glucosidase) in the hydrolysis. Emulsin, obtained from prune seeds, hydrolyzes *beta* glucosides in general.



Lactose, also called milk sugar, is obtained from milk. Hydrolysis gives one mole of glucose and one of galactose. Complete methylation and identification of the hydrolysis products of octamethylactose show lactose to be a galactosidoglucose, with the attachment at the 4-position of glucose. Although the glycosidic linkage is *beta*, emulsin fails to hydrolyze lactose, since it is a galactoside, not a glucoside.

Lactose, having a free hemiacetal group, exists in two anomeric forms, gives osazones, and reduces Benedict's reagent and Fehling's solutions.

(6) *Other Oligosaccharides.* A number of higher oligosaccharides are known to occur in nature. The most important of these is raffinose, which is widely distributed in plants. Partial hydrolysis of this sugar gives a mixture of glucose, galactose, fructose, sucrose, and melibiose. The last of these is 6- β -D-galactopyranosido-D-glucopyranose, an isomer of lactose. Raffinose is not a reducing sugar, hence all the hemiacetal groups of the constituent monosaccharides are utilized in the glycosidic linkages. Formation of both sucrose and melibiose, which have the glucose unit in common, indicates that the order of connection is galactose to glucose to fructose. Accordingly, raffinose is 6- β -D-galactopyranosido- α -D-glucopyranosido- β -D-fructofuranose.



E. Polysaccharides

(1) *Cellulose.* Cellulose is an important constituent of woody plants, in which it serves a structural function. Plants manufacture cellulose from

their store of photosynthetic glucose. Wood is cellulose embedded in lignin, a polymeric, phenolic ether-alcohol. Cotton, filter paper, and facial tissue are nearly pure forms of cellulose.

Molecular weight determinations on cellulose give widely varying values depending on the source and treatment of the cellulose. There is no possibility of a molecular weight determination on native cellulose, since the material must be treated in some way to bring it into a dispersed form, as well as to separate it from noncellulosic material. As a limiting value, however, the average molecular weight of native cellulose is estimated to be at least 650,000. Estimates of molecular weights ten times this value have been proposed. After treatment with various agents to break wood down into pulp, the cellulose has an average molecular weight of about 75,000.

Prolonged heating of cellulose with acids ultimately evolves glucose and its dehydration products. Cellulose is indigestible to humans, as we have no enzyme capable of hydrolyzing it. However, several bacteria do have the necessary enzymes, hence can utilize cellulose as a source of metabolic carbohydrate. Termites and cattle can utilize cellulose because of symbiotic bacteria in their digestive tracts.

Because of its resistance to hydrolysis, cellulose is readily esterified by strong acids. A mixture of concentrated nitric and sulfuric acids reacts to give polynitrates of cellulose. There are three free hydroxy groups present in each glucose unit in the cellulose molecule, so that, theoretically, a cellulose trinitrate is possible. Because cellulose trinitrate is unstable in storage and detonates upon striking, it is not useful commercially. A nitrate containing between one and two nitrate groups per glucose unit is called *pyroxylin*. An ether-ethanol solution of this, called *collodion*, was used in the preparation of the first industrially important synthetic plastic, celluloid. Because of its high flammability, celluloid has been replaced by other plastics. Cellulose nitrate with the somewhat higher proportion of two to two and one-half nitrate groups per glucose unit is used as an explosive for blasting and as a component of smokeless gunpowder. This material, often called *nitrocellulose*, when plasticized with glyceryl trinitrate is *double base powder*, the usual propellant for rifle and cannon ammunition.

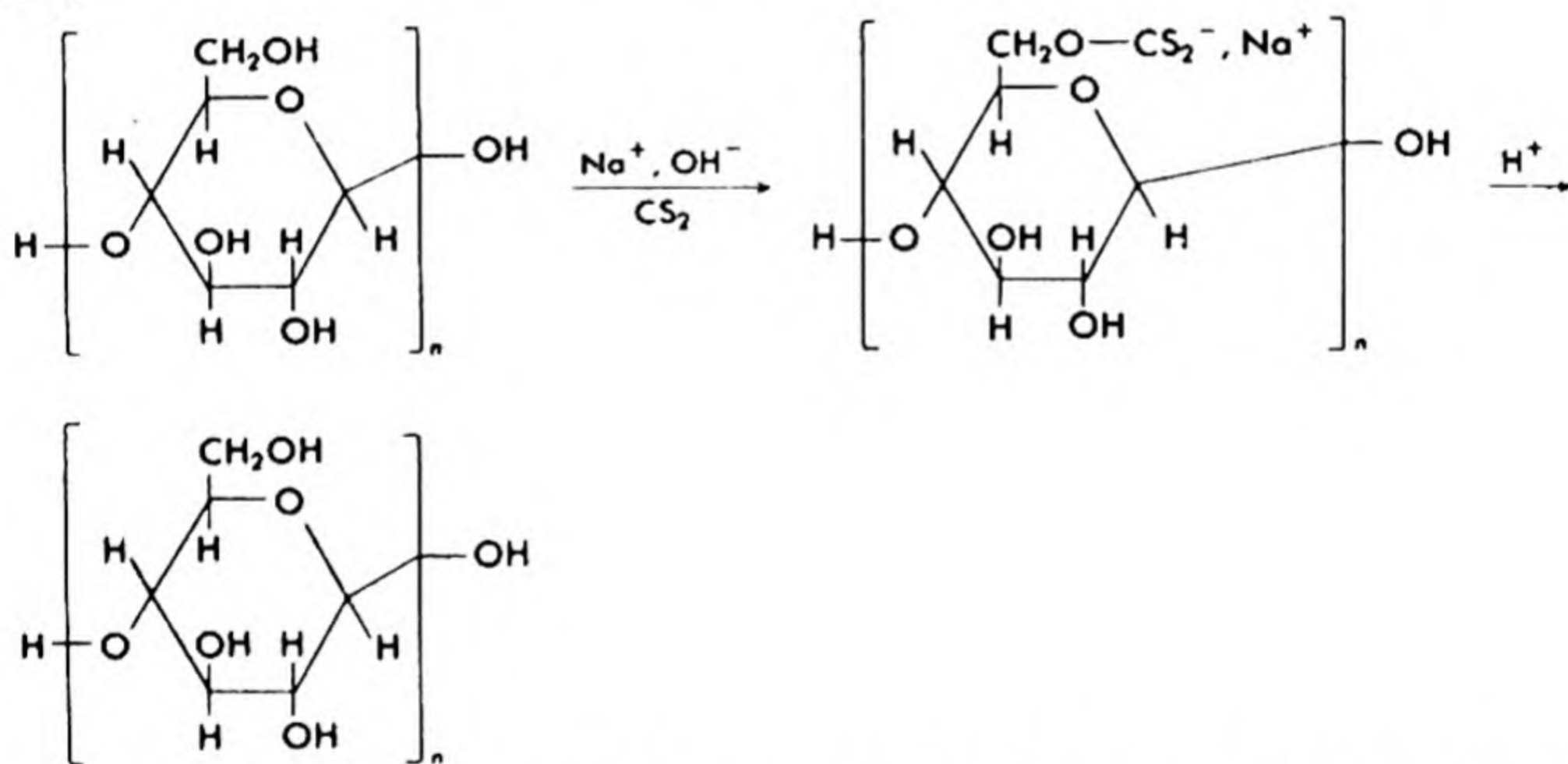
Treatment of cellulose with acetic anhydride in the presence of glacial acetic acid and a little sulfuric acid or zinc chloride gives acetates with one to three acetyl residues per glucose unit. The product is not as uniform as the nitrate, since acetic anhydride does not enter the fibrous micelle of cellulose as easily as nitric acid does. Hence, the acetate must be purified by dissolving in acetone and filtering before it can be fabricated into useful articles.

In contrast to the nitrate, cellulose acetate burns only when held in contact with a flame. This advantage offsets its somewhat greater expense in the manufacture of films for projection, where the intense radiant heat is likely to ignite cellulose nitrate. Cellulose acetate can be made into many forms by pressing, molding, or extruding. Acetate is used in large amounts as a textile fiber.

Recently, mixed esters of cellulose, such as cellulose acetate butyrate, have found special applications because of specific properties such as toughness (laminated safety glass) or dielectric strength (electrical insulation).

Another cellulose ester of commercial importance is cellulose xanthate. Treatment of cellulose with a mixture of aqueous sodium hydroxide and carbon disulfide gives a viscous aqueous solution of cellulose xanthate, called *viscose*. Acidification of the viscose solution precipitates cellulose that is only physically different from the original material (outline 23). Extrusion of viscose through spinnerets into an acid solution gives *rayon*, while extrusion as a film gives *cellophane*.

(23)

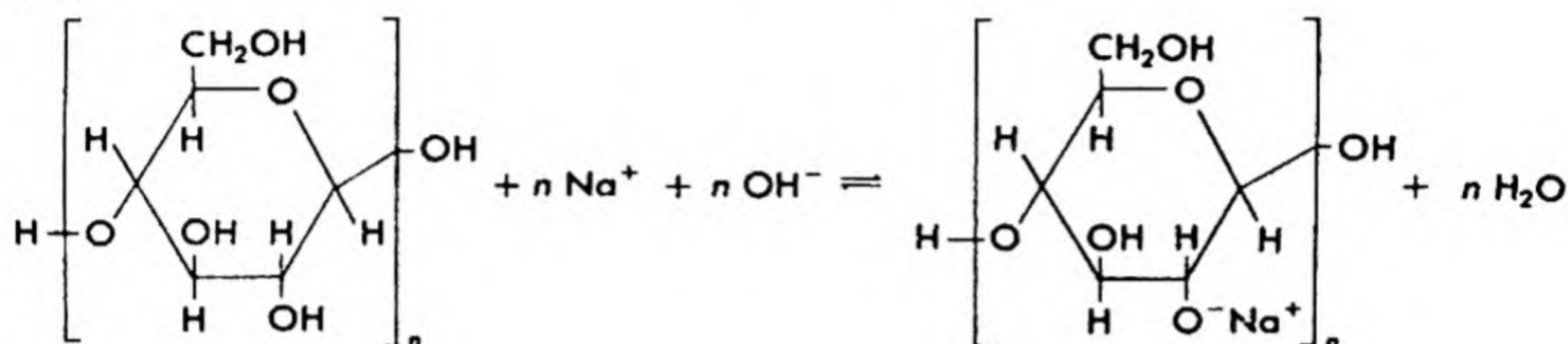


Like monosaccharides and oligosaccharides, cellulose can be methylated by treatment with methyl sulfate and sodium hydroxide. The product, *methyl cellulose*, forms emulsoids with water and is useful as an emulsifier, sizing agent, and thickener. Ethyl cellulose is also prepared commercially.

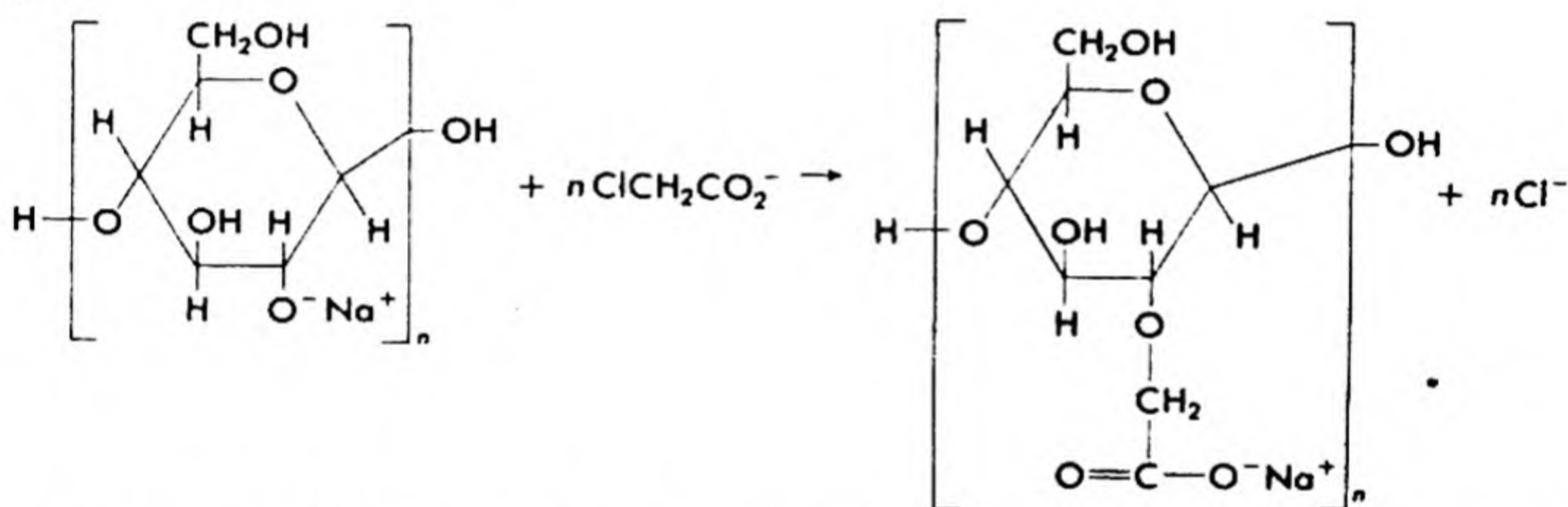
The most interesting cellulose ether, from the commercial viewpoint, is *sodium carboxymethyl cellulose*, also called *cellulose gum*. This ether is prepared by treating alkali cellulose with sodium chloroacetate (eqs. 24 and 25). Cellulose gum has outstanding hydrophilic and gel-forming quali-

ties; only a small per cent in water is sufficient to form a rubbery, tough, adhesive gel. Commercial uses include laundry sizing agent (replacing starch), adhesives, detergent promoter, suspending agent (e.g., in oil drilling muds), soil conditioner, and ceramic glaze binder.

(24)



(25)



Because of its semicrystalline state, cellulose was the first polysaccharide to yield fruitful results in structural studies. Hydrolysis of cellulose to glucose and cellobiose indicates its structural constituents and stereochemical arrangement. Use of x-ray diffraction shows a crystallite structure with slightly overlapped fiber bundles. Between bundles are somewhat disarranged, amorphous regions (Fig. 38-2). Cellulose molecules are

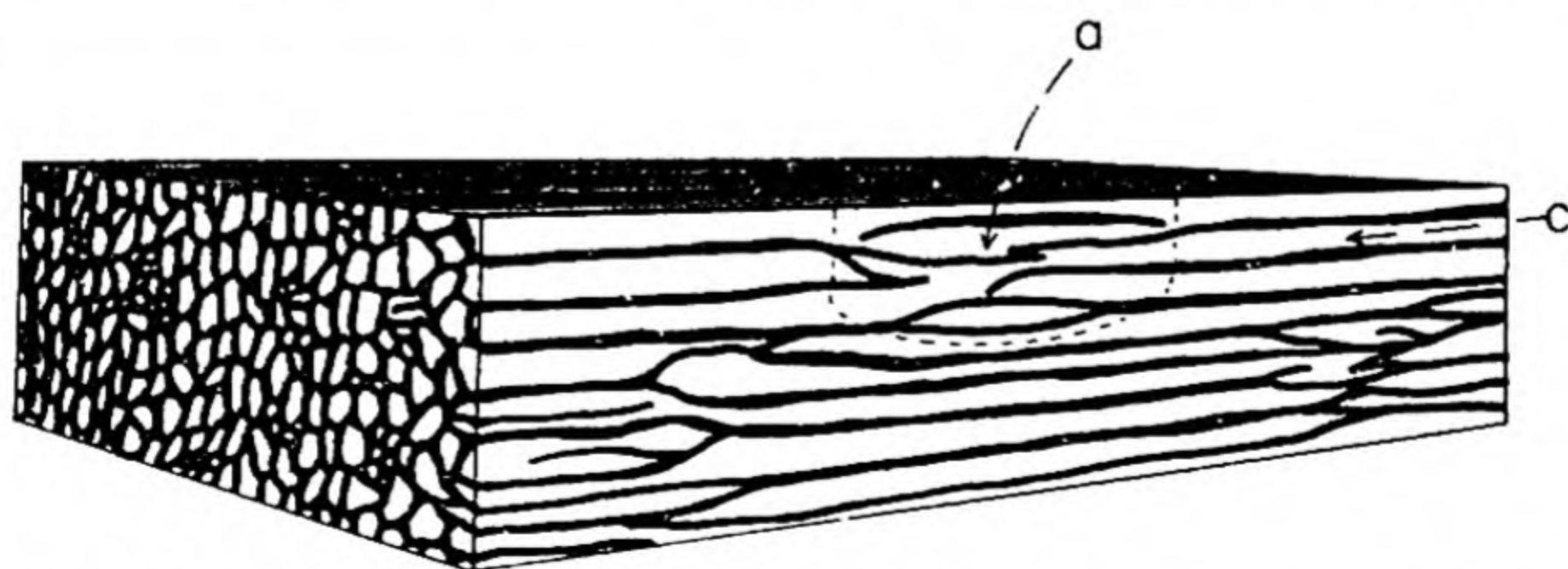


Fig. 38-2. Fibrous structure of cellulose. (a) Amorphous region, (c) Crystalline region.

long, continuous chains of glucose units, without branching or cross-linking other than hydrogen bonding. The *beta* glycosidic linkages allow the units to lie out straight, giving maximum contact between contiguous chains.

(2) *Starch*. Starch is the form in which nearly all plants store carbohydrate for metabolic use by the plant embryo in seeds and for the natural hibernation or drought periods. In animals, a similar material called *glycogen* is stored in liver and muscles. Although starch from widely distributed plant sources is chemically similar, starch should be considered not as a compound, but as a class of compounds, since the molecular arrangement, molecular weight, and granular form vary with the source.

Even starch from a single source is inhomogeneous. Native starches can be separated into two fractions by boiling the starch in aqueous butanol and allowing the suspension to cool. The precipitated portion is termed *amylose* or insoluble starch fraction. The suspended portion is called *amylopectin* or soluble starch fraction.

Amylose ranges in molecular weight from 10,000 to 100,000. Its solubility in water varies considerably with its past history from more soluble than amylopectin to considerably less soluble. Amylopectin has molecular weights in the range from 50,000 to 6,000,000. Its concentrated suspensions in water are gels. Both forms of starch are optically active with specific rotations between $+160^\circ$ and $+220^\circ$.

Whole starch and both starch fractions are swelled to several times their dry volume upon soaking in water. This indicates that hydrogen bonding forces between starch molecules are much weaker than those between cellulose molecules.

Chemical properties of starch are similar to those of cellulose, except that starch is much more easily hydrolyzed by acid solutions. Degradation of starch is thus significant during esterification.

Treatment of starch with methyl sulfate and alkali gives completely methylated starch, a material important to the structural analysis of starch.

The use of starch as an indicator for free iodine, or of iodine as an indicator for starch, is one of the more familiar of the chemical reactions of starch. The intensely blue-black complex is a *clathrate*, or cage-like complex between iodine and amylose. Diffraction studies have confirmed that iodine molecules are enfolded in helical coils of the starch chain. Pure amylopectin gives no blue color with iodine, but does give a weak red to purple color.

Starch can be fermented biologically in a variety of ways to give useful commercial products. Besides ethanol and the accompanying amyl alcohols, different organisms produce butyric acid, butyl alcohol, and acetone,

Because of the more heterogeneous and more complex nature of starch, analysis of its structure was achieved much later than that of cellulose. The formation of tough films by acetates and nitrates of amylose suggested cellulose-like linearity of the chains. Further confirmation of this is the complete conversion of amylose to maltose by β -amylase and the formation of trimethylglucose, with but a trace of tetramethylglucose, by hydrolysis of completely methylated starch. The formation of maltose and the structure of the trimethylglucose indicate that insoluble starch has glycosidic linkages on the 4-positions of the glucose units. Complete hydrolysis of amylose to glucose by α -glucosidase (maltase) shows the glycosidic bonds all to be *alpha*.

Amylopectin and glycogen are quite similar in properties and structure. Their acetates and nitrates form only brittle masses upon compacting or powders upon attempted extrusion into sheets or fibers. These properties suggest nonlinearity.

Only about half of the glucose units are degraded from amylopectin by β -amylase. The molecular residues form a substance called dextrin-I. α -Glucosidase then attacks the next 9% of the glucose units, based on original material, to give dextrin-II. This is again attacked by β -amylase to degrade another 16% of the glucose units, giving dextrin-III. This behavior shows irregularities along the starch chains which can only be explained by chain branching. In confirmation, hydrolysis of completely methylated soluble starch fraction gives about 5 mole % of 2,3,4,6-tetramethylglucose, 5 mole % of 2,3-dimethylglucose and a balance of about 90 mole % of 2,3,6-trimethylglucose.

Such evidence indicates that soluble starch and glycogen have branching structures with 25-28 glucose units per branch in starch, 12-18 in glycogen. That the structure has tree-like multiple branching is shown by the fact that β -amylase does not complete the degradation after α -glucosidase removes the first branch stumps. The proposed structure for amylopectin is given in Fig. 38-3. Each small ellipse in the figure represents a glucose unit. As in amylose, most of the glycosidic linkages are attached to the 4-position of adjacent glucose units, but at the branch points, glycosidic linkages are also on the 6-position. Presence of a trace of 3,6-dimethylglucose in the methylamylopectin hydrolyzate may mean that a few of the branches have attachments at the 2-position.

Dextrins are partly hydrolyzed starches. Besides those dextrins produced by selective enzyme action, some are produced by incomplete acid hydrolysis, others by autoclaving starch with water. A dextrin solution prepared by the last method is used as the adhesive mucilage.

(3) *Other Higher Carbohydrates.* The structural foundations of green leaves, pods, stems, and pithy parts of plants are similar to cellulose, but are much more easily hydrolyzed by acids. Furthermore, some of this

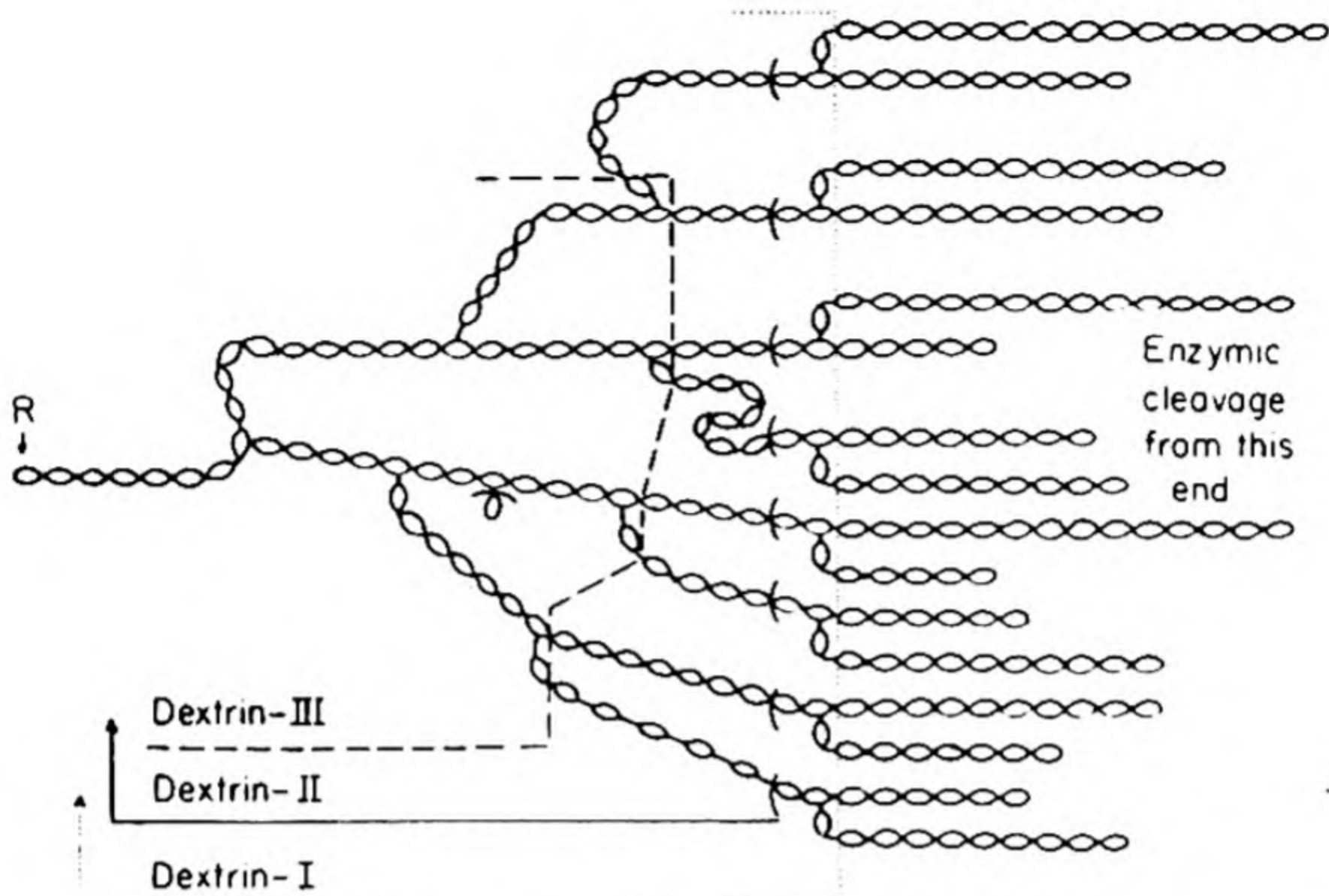
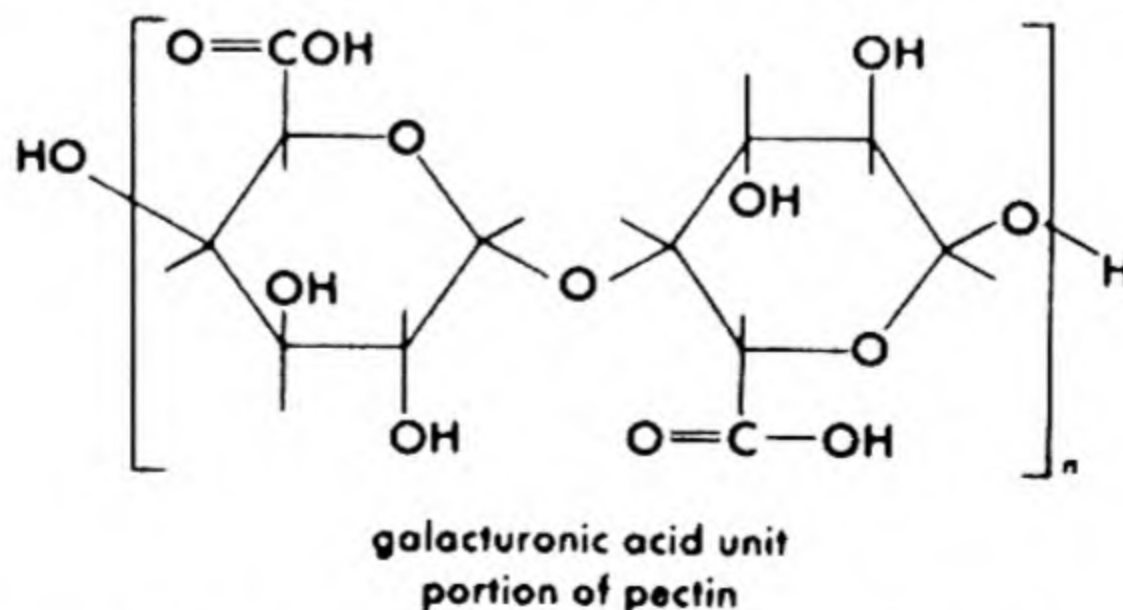


Fig. 38-3. Schematic Representation of Amylopectin Molecule., limit of initial degradation by β -amylase and boundary of dextrin-I; ----, limit of second degradation by β -amylase, and boundary of dextrin-III; (represents limit of degradation of α -glucosidase to give dextrin-II. R, a terminal reducing group.

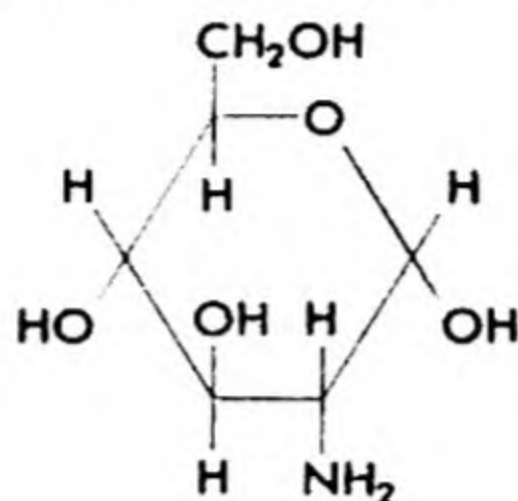
structural material contains pentose units instead of hexose units. These materials are known as *hemicelluloses*. Depending on the type of monosaccharide produced upon hydrolysis, the hemicelluloses are termed pentosans or hexosans.

Pectins are polysaccharides present in green fruits and fruit peelings. These are made up of α -galacturonic acid units with smaller amounts of galactose and arabinose. Pectin methyl esters (commercial pectin) form stiff gels with solutions containing sucrose and fruit acids.



Agars used as media for bacterial growth are polysaccharides obtained from seaweeds. One of these, agar agar, is a galactan.

Chitin is the organic constituent of the hard covering of insects and crustacea. This polysaccharide is hydrolyzed to 2-glucosamine and acetic



2-glucosamine

acid. Other biological materials containing glucosamine units are the mucin of saliva and the mucoids of connective tissue. Glucosamine is also present in hyaluronic acid, a constituent of vitreous humor (interior of the eye) and synovial fluid (joint and muscular lubricant).

38-2 METABOLISM OF CARBOHYDRATES

A. Digestion and Utilization

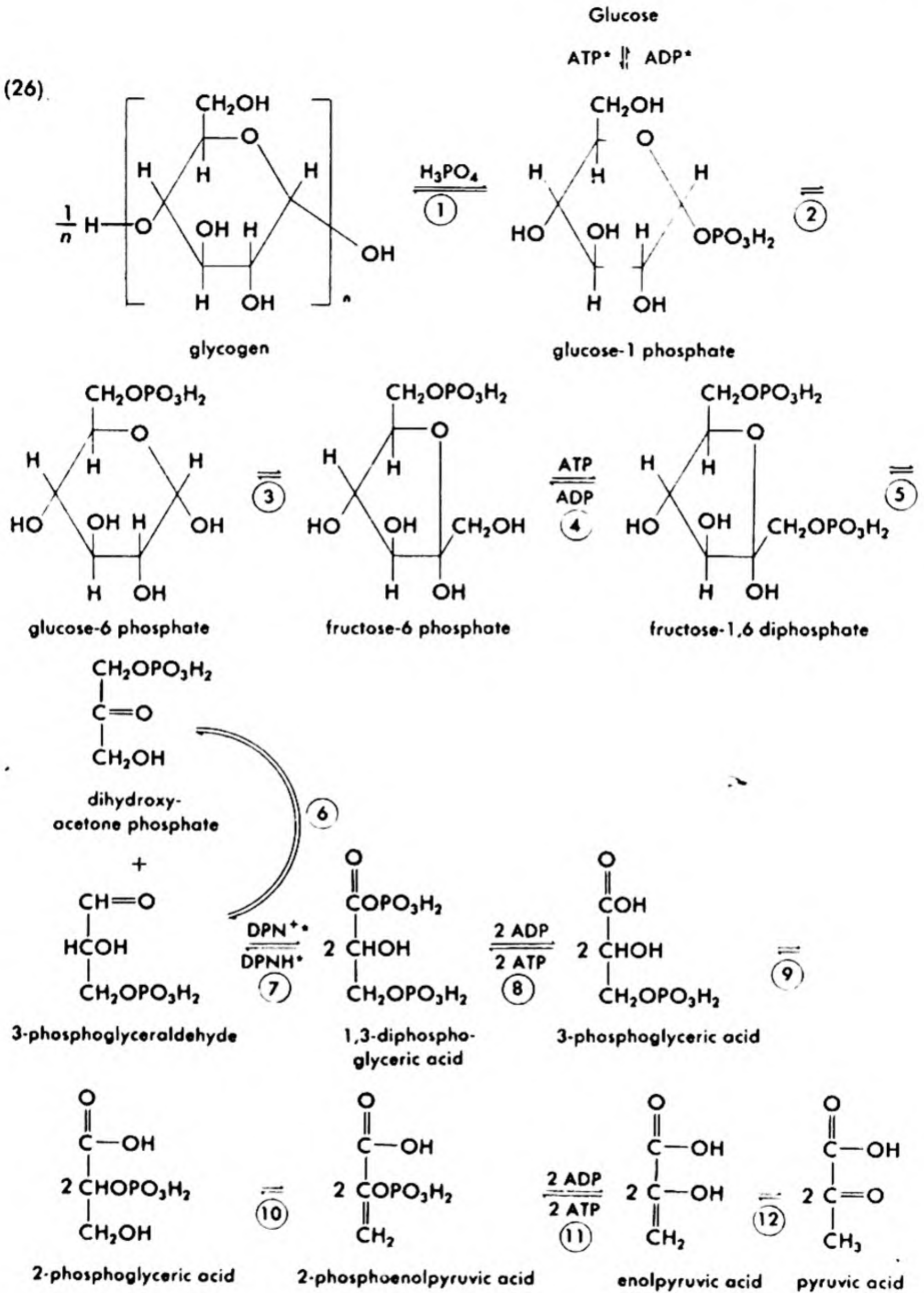
Digestion of starch, glycogen, and disaccharides involves the hydrolysis of the α -glucosidic linkages of these materials to form monosaccharides, of which glucose is the most important. β -Glucosidic carbohydrates, such as cellulose, remain indigestible to vertebrates. After digestion, the monosaccharides are absorbed into the blood stream and carried to the cells where they are to be used.

Since liver tissues have the ability to interconvert galactose, glucose, and fructose, and perhaps other hexoses, the problem of the storage and utilization of these energy sources can be considered a problem of the utilization of glucose.

Carbon dioxide and water are the biological oxidation products of glucose under normal quiescent conditions. During vigorous exercise, when more glucose is degraded than can be oxidized by the oxygen stored in the cells, lactic acid is the end product. The metabolism of glucose is a complex process involving well over a score of separate reactions, each catalyzed by a different enzyme. Outline (26) gives the course for the degradation of glucose to pyruvic acid. This series of reactions, called the glycolytic sequence, precedes the formation of lactic acid or of products leading to carbon dioxide in vertebrates, ethanol in yeast, and many other fermentation products.

The glycolytic sequence from glucose synthesizes 2 moles of adenosine triphosphate, the immediate energizing agent for muscular contractions and many other biological processes.

Reduction of pyruvic acid to lactic acid serves as a means of regenerating diphosphopyridine nucleotide (coenzyme-I) for the oxidation of di-

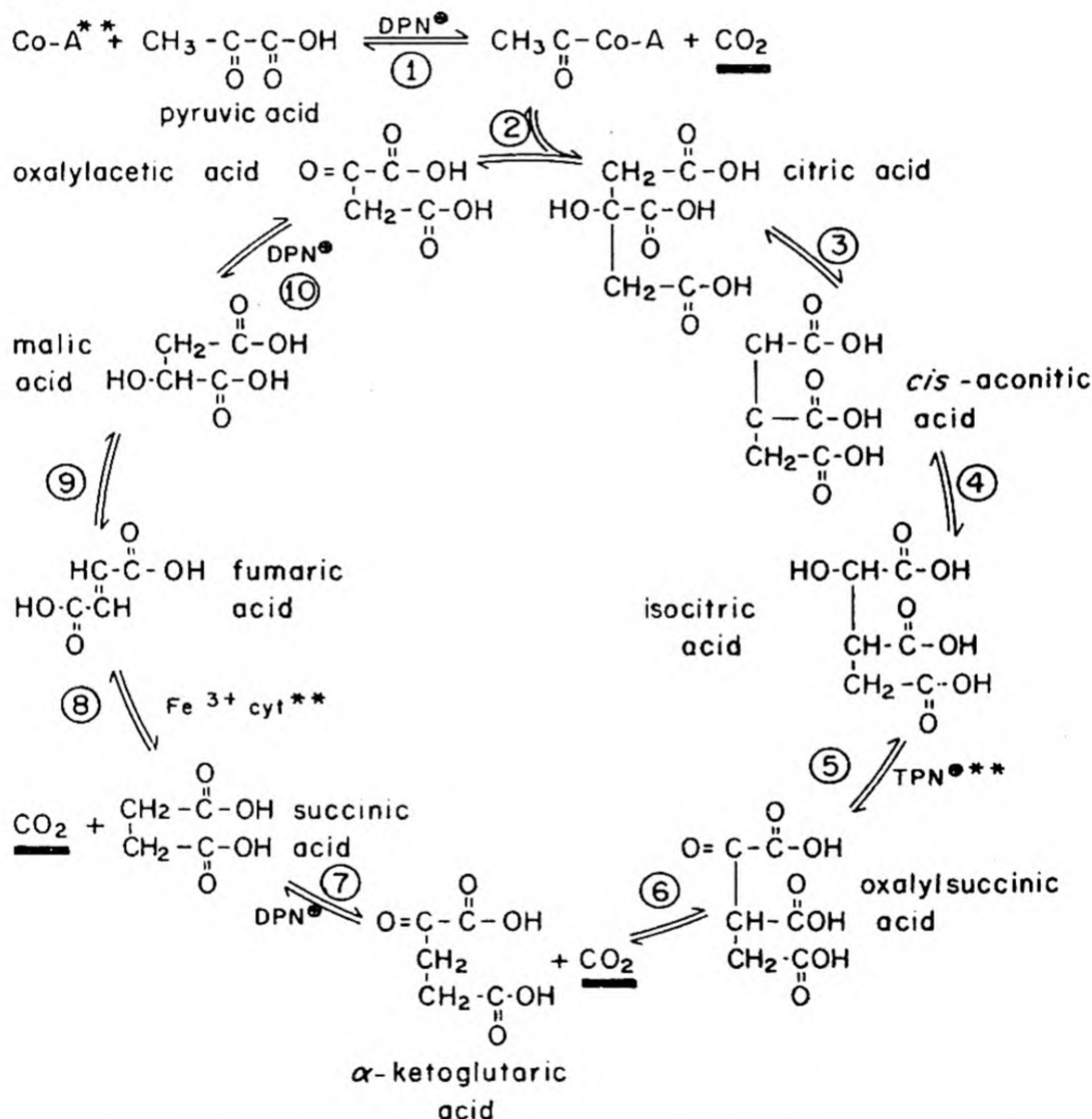


* ATP is adenosine triphosphate, a coenzyme. The net synthesis of 2 moles (starting with glucose) of this from ADP, adenosine diphosphate, is the biological purpose of the glycolytic sequence. DPN⁺ is diphosphopyridine nucleotide or coenzyme-I, an oxidizing coenzyme. DPNH is reduced form. (See §39-3 and §39-3B.)

phosphoglyceraldehyde to diphosphoglyceric acid (step 7) when cytoplasm is depleted of oxygen.

Outline (27) shows the path by which pyruvic acid is oxidized ultimately to carbon dioxide and water. This is the Krebs (Nobel laureate, 1953) citric acid cycle, the disclosure of which in 1937 ranks along with Fischer's carbohydrate studies and Ehrlich's discovery of chemotherapy as one of the outstanding contributions to the field of biochemistry.

(27)



**CoA is coenzyme A. TPN⁺ is triphosphopyridine nucleotide. Fe³⁺ cyt is ferric cytochrome (see §39-3B).

B. Photosynthesis

Perhaps the one common characteristic of all green plants is their utilization of chlorophyll to convert energy from sunlight for the synthesis of carbohydrates from carbon dioxide and water. All members of the animal kingdom are dependent on this plant source of metabolic energy. The chlorophyll is a magnesioporphyrin (§42-21) the role of which is to utilize energy from red light radiation to reduce thioctic (lipoic) acid. This in turn reduces (through a sequence of reactions) phosphoglyceric acid to phosphoglyceraldehyde.

The sequence of reactions in photosynthesis has been probed ever since Joseph Priestly first observed the evolution of oxygen by illuminated plants in 1772. A multitude of eminent scientists have contributed. The most significant recent contributions were EPR studies by Barry Commoner's group at Washington University, showing the production of unpaired electrons in chlorophyll by light, and isotope tracer studies by Melvin Calvin's (Nobel laureate, 1963) group at the University of California, establishing the intermediates in carbon dioxide fixation. Outline (28) shows the main photosynthetic mechanism. An alternate mechanism via glycolic acid has been observed by Howard A. Tanner and associates of the Charles F. Kettering Foundation.

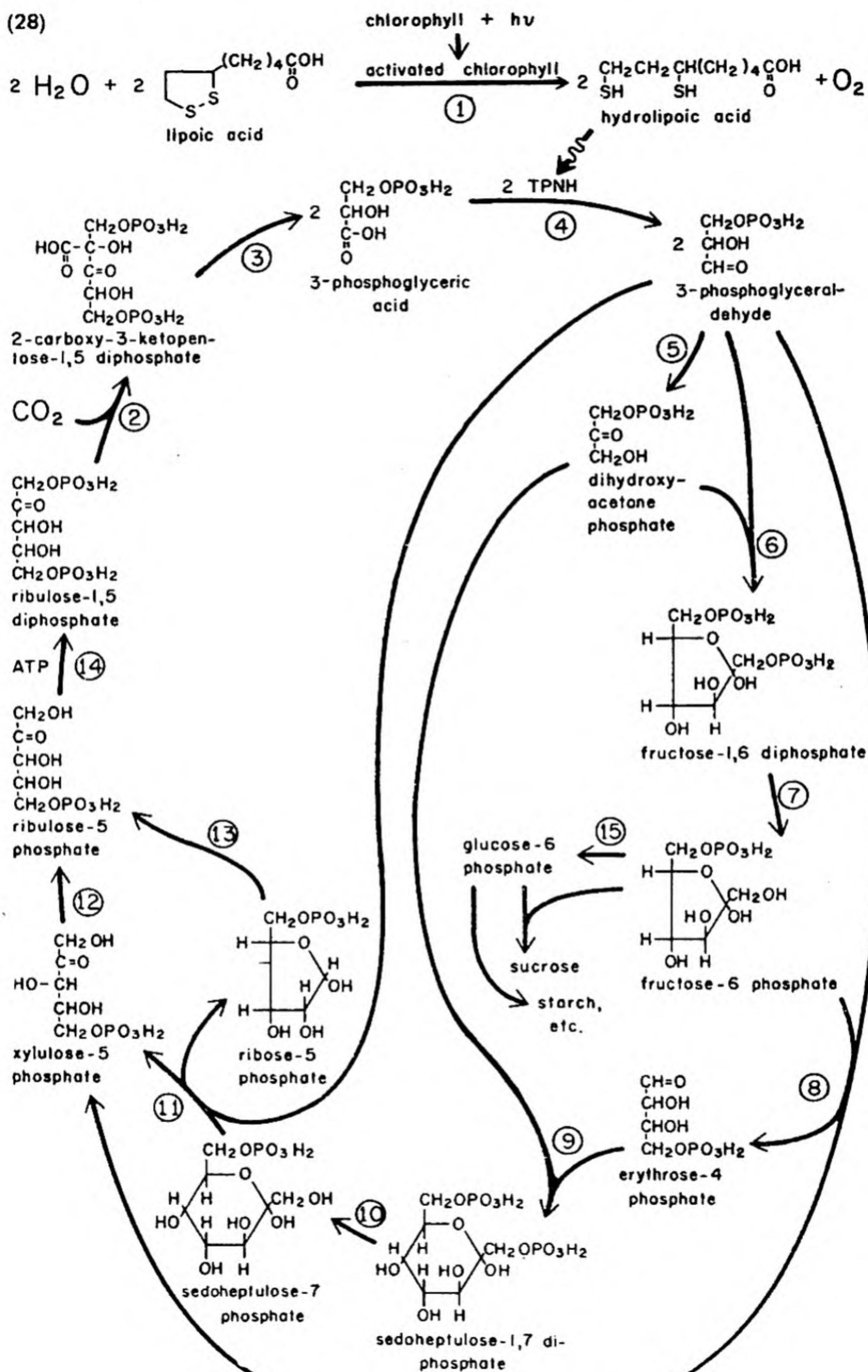
The structures of the coenzymes involved in glucose metabolism are discussed in §39-3B. A coenzyme is the active, nonpeptide part of an enzyme or biological catalyst.

38-3 CONSTITUENTS OF WOOD

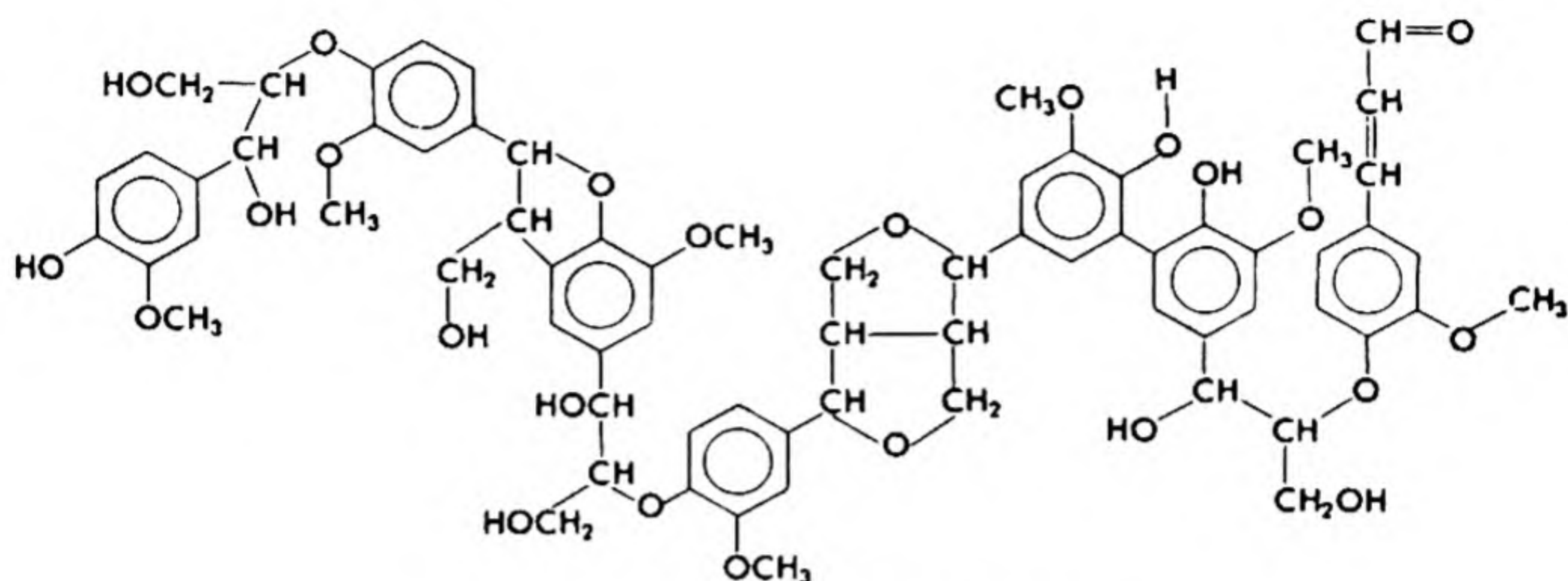
Only 35-40% of "dry" pulp wood is cellulose. The balance of wood consists of hemicelluloses (5-25%), lignin (20-40%), resins and oils (1-15%), glycosides (1-10%), water (10-13%), proteins (1-2%), and inorganic salts (about 1%). Two and one-half tons of pulpwood are required to make a ton of paper pulp, air-dried. Part of the loss is due to degradation of cellulose in the pulping process.

Lignin is a complex polymeric material which apparently acts as the binding material cementing the cellulose and other polysaccharide fibers together to form the wood structure. The specific nature of the lignin polymer varies with the wood source, but skeletal units consist largely of three-carbon chains attached to guaiacol, catechol, phenol, or similar aromatic rings. A structural portion based upon coniferyl alcohol is shown below. It would appear that the biogenetic course of the formation of lignin involves an enzymatic oxidation of coniferyl alcohol (or a similar material) to a free radical such as V (of which only two of the several valence-bond structures are shown). These radicals may couple or react

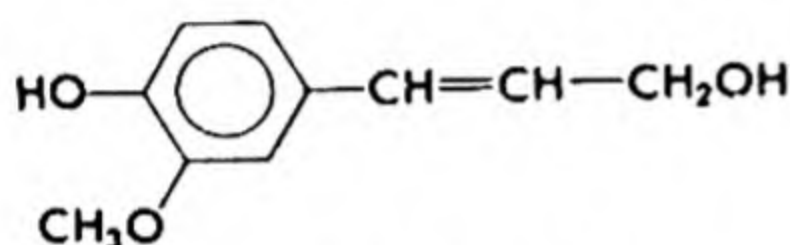
(28)



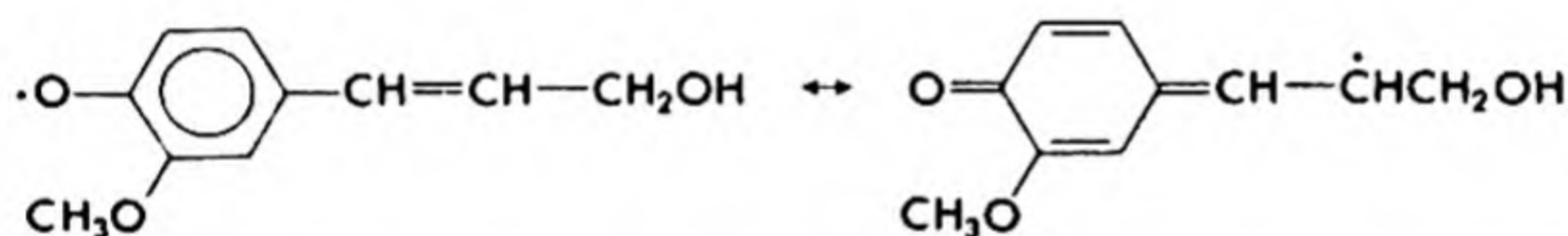
with other coniferyl alcohol molecules in typical free radical reactions to give the lignin polymer.



a suggested formula for a lignin fragment



coniferyl alcohol



V

SUPPLEMENTARY READINGS

- Freudenberg, K., "Lignin: Its Constitution and Formation from *p*-Hydroxycinnamyl Alcohol," *Science*, **148**, 595 (1965).
- Hassid, W. Z., "Starch," in H. Gilman, *Organic Chemistry, an Advanced Treatise*, Vol. IV, Wiley, New York, 1953, pp. 901-950.
- Heuser, E., *Carbohydrates III-Cellulose*, in H. Gilman, *Organic Chemistry, an Advanced Treatise*, Vol. II, Wiley, New York, 1953, pp. 1664-1719.
- Pearl, I. A., "Lignin Chemistry, Century-Old Puzzle," *Chem. Eng. News* **42**, No. 27, 80-93 (July 6, 1964).
- Percival, E. G. V., *Structural Carbohydrate Chemistry*, 2nd Ed., Miller, London, 1962.
- Pigman, W. W., ed., *The Carbohydrates. Chemistry, Biochemistry, Physiology*, Academic Press, New York, 1957.
- Raymond, A. L., "Carbohydrates II," in H. Gilman, *Organic Chemistry, an Advanced Treatise*, 2nd Ed., Vol. II, Wiley, New York, 1943, pp. 1605-1663.
- Wolfram, M. L., "Carbohydrates I," in H. Gilman, *Organic Chemistry, an Advanced Treatise*, 2nd Ed., Vol II, Wiley, New York, 1943, pp. 1532-1604.

QUESTIONS AND PROBLEMS

1. Give an explanation, illustration, or definition to show clearly what is meant by each of the following terms. Supplement diagrams with verbal explanation.

- | | |
|-------------------|------------------|
| a. monosaccharide | f. mutarotation |
| b. disaccharide | g. epimers |
| c. polysaccharide | h. anomers |
| d. carbohydrate | i. pyranose ring |
| e. reducing sugar | j. furanose ring |

2. Write configurational formulas for specific compounds that illustrate the following terms. In each case, explain how the formula illustrates the term.

- | | |
|----------------|--------------------|
| a. aldohexose | f. glycoside |
| b. ketohexose | g. aldonic acid |
| c. ketotriose | h. glycaric acid |
| d. aldohexose | i. glycuronic acid |
| e. ketopentose | j. osazone |

3. Tell which of the following compounds are *not* carbohydrates and why.

- | | |
|---|---|
| a. erythrose, $C_4H_6O_4$ | d. 2-hydroxyethanal, $C_2H_4O_2$ |
| b. cyclohexanhexol (inositol), $C_6H_{12}O_6$ | e. ethanoic acid, $C_2H_4O_2$ |
| c. erythritol, $C_4H_{10}O_4$ | f. 2,3,4-trihydroxypentanal, $C_5H_{10}O_4$ |

4. Write equations for the reactions used to prove the structure of glucose: cyanohydrin formation, hydrolysis of the cyanohydrin, hydrogen iodide reduction. Write equations for the same reactions starting with fructose. Compare the products.

5. Write equations for the following reactions. Use configurational formulas for carbohydrates and their derivatives. Indicate essential conditions.

- | | |
|--|--|
| a. complete methylation of glucose | f. preparation of four aldohexoses from tagatose, a ketose related to galactose in the same way fructose is related to glucose |
| b. formation of methyl glucoside from glucose | g. preparation of three aldohexoses from fructose |
| c. formation of phenylglucosazone from mannose | h. preparation of diacetoneglucofuranose from glucose |
| d. hydrolysis of pentamethylglucose | |
| e. oxidation of mannose to mannonic acid (an aldonic acid) | |

6. Write equations showing why D(+)-glucose and D(-)-fructose produce the same phenylosazone. Use configurational formulas.

7. Show how the following transformations can be accomplished. Use configurational formulas for carbohydrates and their derivatives. Indicate inorganic reagents and conditions.

- a. ribulose from the suitable aldo-tetrose
 - b. sedoheptulose from altrose
 - c. ribose from glucose
 - d. a meso glycaric acid from an aldohexose
 - e. an optically active glycaric acid from an aldohexose
8. Distinguish between racemization and mutarotation.
 9. Which tetrose gives an optically active glycaric acid upon oxidation? Write the equation to verify your answer.
 10. Show (1) how many stereoisomers and (2) how many optically active forms are possible in the following compounds.
 - a. aldohexopyranoses
 - b. 2-ketohexoses, open form
 - c. pentaric acids (pentose glycaric acids)
 11. An aldohexose obtained by Kiliani's synthesis from talose gives a meso glycaric acid upon oxidation. Write the configurational formula of the aldohexose.
 12. Write equations for any reactions that occur among the reagent mixtures listed below. Use configurational formulas for carbohydrates and their derivatives. Indicate essential conditions. If no reaction occurs, write formulas of reagents and NR.
 - a. fructose + benzoyl chloride
 - b. sucrose + Fehling's solution
 - c. mannose + phenylhydrazine
 - d. lactose + hydroxylamine
 - e. octamethylsucrose + dilute hydrochloric acid
 13. Tell all that is shown about the initial organic reagents by the following reactions.
 - a. $C_5H_{10}O_4 + \text{acetic anhydride} + \text{sodium hydroxide} \rightarrow C_9H_{14}O_6$
 - b. $C_8H_{16}O_6 + H_2O \xrightarrow{\text{emulsin}} C_6H_{12}O_6$
 - c. $C_7H_{14}O_6 + H_2O \xrightarrow{\text{lactase}} C_6H_{12}O_6$
 - d. $C_{12}H_{22}O_{11} + \text{methyl sulfate} + \text{sodium hydroxide} \rightarrow C_{20}H_{38}O_{11} \xrightarrow[HCl]{H_2O} \text{2,3,4-trimethylglucose} + \text{2,3,4,6-tetramethylmannose}$
 - e. $C_6H_9O(OCH_3)_3 \xrightarrow{HCl} C_6H_{10}O_2(OCH_3)_2 \xrightarrow{KMnO_4} \text{2,3-dimethoxyglutaric acid, acetic acid, and 3,4-dimethoxy-5-ketohexanoic acid}$
 14. Explain why sucrose and raffinose are not reducing sugars.
 15. Show how the following compounds can be distinguished by simple laboratory tests. Describe the observed results.
 - a. sucrose and maltose
 - b. cellulose and starch
 - c. cellulose nitrate and cellulose acetate
 - d. viscose rayon and polyester fiber
 - e. galactose and lactose
 - f. soluble starch fraction and insoluble starch fraction

16. Write equations for the acetylation, nitration, and xanthate formation of cellulose.

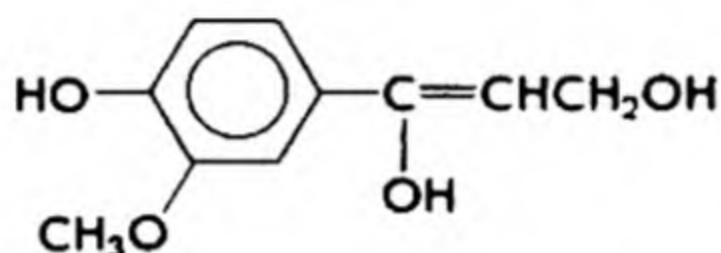
17. Formulate the complete methylation of the following substances and the hydrolysis of the methylated products. Indicate clearly the formation of the several possible methylglucoses.

- | | |
|------------------------------|----------------------------|
| a. cellulose | c. soluble starch fraction |
| b. insoluble starch fraction | |

18. Show how the following syntheses can be accomplished in good yield. Indicate necessary reagents and conditions.

- | | |
|------------------------|--------------------------------|
| a. glucose from starch | c. pyrogallol from tannic acid |
| b. maltose from starch | d. furfuraldehyde from xylose |

19. Show how all the types of bonds present in the lignin unit in §38-3 can be produced from coniferyl alcohol or from hydroxyconiferyl alcohol.



hydroxyconiferyl alcohol

20. How would the empirical analysis of the product of acid-catalyzed reaction of glucose with methanol differ from that observed, if glucose reacted in the aldehyde form rather than the hemiacetal form?

21. What would be the nature of the infrared absorption spectrum of glucose in the 5-6 μ region, (a) if glucose had principally the hydroxy aldehyde structure, (b) if it were principally a mixture of hemiacetals? (The latter is observed.)

22. Write equations to show how tetramethyl glucose can be converted to a trimethoxyglutaric acid by oxidation and to show how the corresponding methylated fructose can be converted to a dimethoxysuccinic acid.

23. (a) Discuss, from a mechanistic point of view, why mutarotation is both acid catalyzed and base catalyzed. (b) Why are the formation and hydrolysis of methyl glucoside (eq. 2) acid catalyzed, but not subject to base catalysis?

24. Give a reasonable reaction path for the formation of furfural from xylose, using your knowledge of acid-catalyzed reactions.

25. Write the structural formulas involved in the Haworth proof of structure of sucrose.

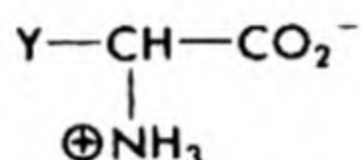


Amino Acids and Proteins

39-1 AMINO ACIDS

A. Classification

Amino acids are, as the name suggests, organic acids having amino groups. With few exceptions, amino acids from natural sources are *alpha*-aminocarboxylic acids



an α -aminocarboxylic acid

Some exceptions are β -aminopropionic acid (β -alanine) from pantothenic acid, β -aminoethanesulfonic acid (taurine) from bile salts, and *p*-aminobenzoic acid.

α -Amino acids of three types occur in nature. The simplest are monoaminomonocarboxylic acids, or neutral amino acids. Diaminomonocarboxylic acids are termed basic amino acids. Monoaminodicarboxylic acids are called acidic amino acids.

Most amino acids are readily synthesized by all living organisms. A few, however, are not synthesized by vertebrates as rapidly as they are utilized metabolically. These must be furnished in the diet, hence they are termed essential amino acids.

B. Sources

Most of the naturally occurring amino acids are obtained by hydrolysis of proteins, one of the principal constituents of biological material. Others are obtained by cleavage of vitamins, hormones (e.g., thyroxine) or other metabolic participants. A few have only transitory existence in living organisms, but can be isolated using specific metabolic enzymes. Ornithine and citrulline are examples of these. A list of certain important amino acids is given in Table 39-1 with appropriate structural formulas. Note that most of them can be considered as derivatives of alanine. The remainder of each of the structures is emphasized by boldface type.

TABLE 39-1. Certain Naturally Occurring Amino Acids

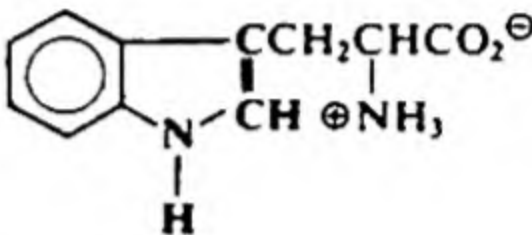
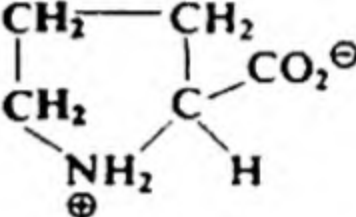
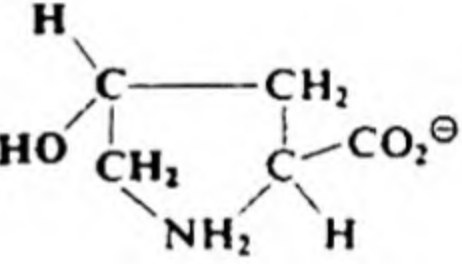
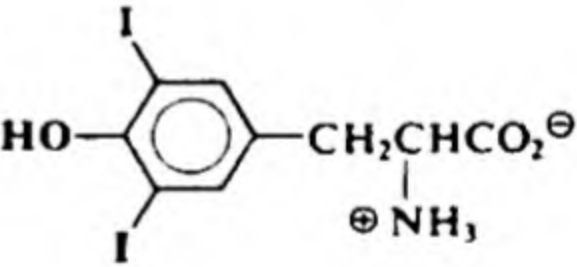
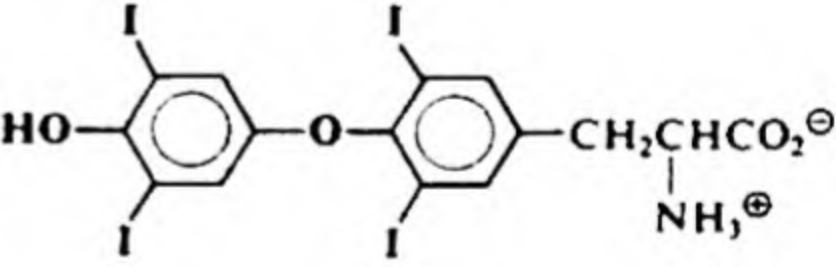
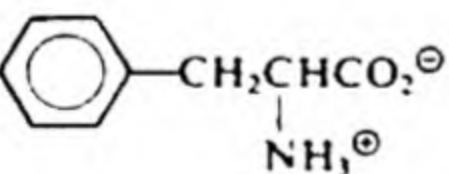
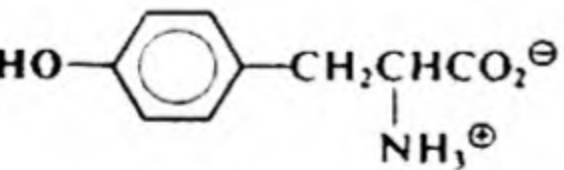
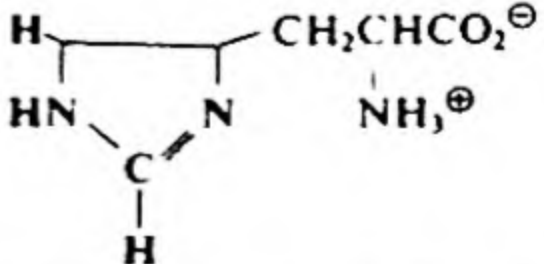
Name	Formula	Name	Formula
NEUTRAL AMINO ACIDS			
Glycine	$\text{CH}_2\text{CO}_2^\ominus$ NH_3^\oplus	L-Methionine ^a	$\text{CH}_3\text{SCH}_2\text{CH}_2\text{CHCO}_2^\ominus$ NH_3^\oplus
L-Alanine	$\text{CH}_3\text{CHCO}_2^\ominus$ NH_3^\oplus	L-Asparagine	$\text{H}_2\text{NCCH}_2\text{CHCO}_2^\ominus$ O NH_3^\oplus
L-Valine ^a	CH_3 CHCHCO_2^\ominus NH_3^\oplus	L-Glutamine	$\text{H}_2\text{NCCH}_2\text{CH}_2\text{CHCO}_2^\ominus$ O NH_3^\oplus
L-Leucine ^a	CH_3 $\text{CHCH}_2\text{CHCO}_2^\ominus$ NH_3^\oplus	L-Tryptophan ^a	
L-Isoleucine ^a	CH_3CH_2 CHCHCO_2^\ominus NH_3^\oplus	L-Proline	
L-Norleucine	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CHCO}_2^\ominus$ NH_3^\oplus	L-Hydroxyproline	
L-Serine	$\text{HOCH}_2\text{CHCO}_2^\ominus$ NH_3^\oplus	L-Iodogorgoic acid	
L-Threonine ^a	OH $\text{CH}_3\text{C}-\text{CHCO}_2^\ominus$ H NH_3^\oplus	L-Thyroxine	
L-Phenylalanine ^a		BASIC AMINO ACIDS	
L-Tyrosine		L-Lysine ^a	$\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CHCO}_2^\ominus$ NH_3^\oplus
L-Cysteine	$\text{HSCH}_2\text{CHCO}_2^\ominus$ NH_3^\oplus	L-Arginine ^a	$\text{H}_2\text{NCNHCH}_2\text{CH}_2\text{CH}_2\text{CHCO}_2^\ominus$ NH_2^\oplus NH_2
L-Cystine	NH_3^\oplus $\text{SCH}_2\text{CHCO}_2^\ominus$ $\text{SCH}_2\text{CHCO}_2^\ominus$ NH_3^\oplus	L-Histidine ^a	

TABLE 39-1. Certain Naturally Occurring Amino Acids (Cont.)

Name	Formula	Name	Formula
L-Ornithine	$\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	L-Glutamic Acid	$\text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{NH}_3^+)\text{CO}_2^-$
L-Citrulline	$\text{H}_2\text{NCN}(\text{H})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	OTHER THAN α -AMINO ACIDS	
ACID AMINO ACIDS		β -Alanine	$\text{H}_3\text{N}^+\text{CH}_2\text{CH}_2\text{CO}_2^-$
L-Aspartic Acid	$\text{HOCH}_2\text{CH}_2\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	Taurine	$\text{H}_3\text{N}^+\text{CH}_2\text{CH}_2\text{SO}_3^-$
		<i>p</i> -Aminobenzoic Acid*	$\text{H}_3\text{N}^+ - \text{C}_6\text{H}_4 - \text{CO}_2^-$

¹Essential for human diet

Several nonbiological methods of synthesis of amino acids have been discussed in various sections of this text. Briefly, these are ammonolysis of α -halogen acids (§12-1C), Strecker's cyanohydrin synthesis (§18-2B), malonic ester and acetoacetic ester syntheses (§21-6A) and reductive ammonolysis of α -ketoacids (§27-1F).

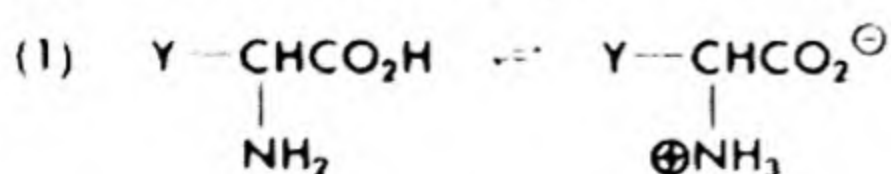
C. Physical Properties of Amino Acids

As might be expected of compounds which have both acidic and basic groups in the same molecule, amino acids give evidence of high polarity. Their melting points are quite high for substances with such low molecular weights (compare glycine, which melts at 236° with decomposition, and glycolic acid, HOCH_2COOH , which melts at 79°). Unusually *low* solubilities for polyfunctional compounds can be explained on the basis of very strong intracrystalline forces. That the low solubilities of some amino acids are not due to nonpolar nature is indicated by their insolubility in nonpolar solvents.

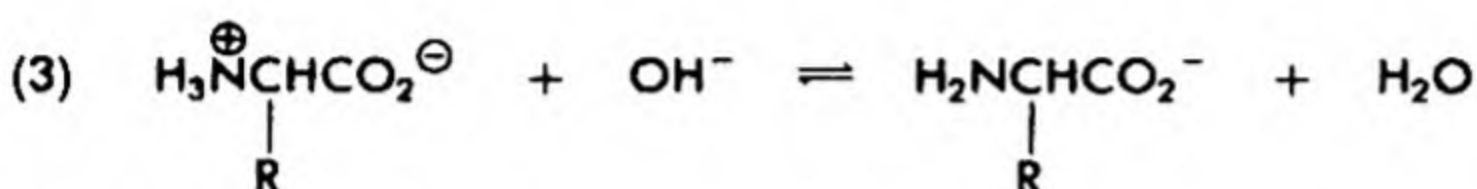
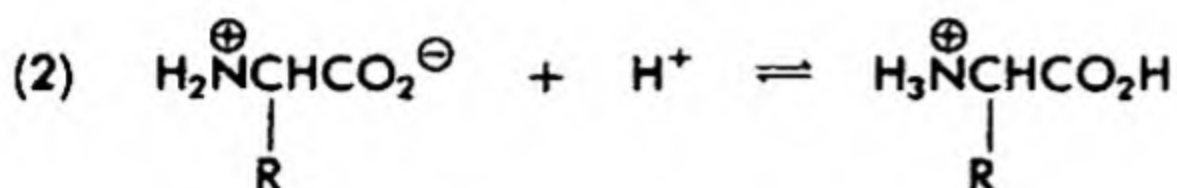
All α -amino acids but glycine are optically active. The naturally occurring ones derived from protein hydrolysates belong to the L-series related to lactic acid (which in turn is based on glyceraldehyde). Some metabolic products of lower organisms contain D-amino acids.

D. Chemical Properties

(1) *Salt Formation and Ionic Behavior.* As is to be expected of compounds with both acidic and basic groups in the molecule, amino acids are amphoteric. Furthermore, considerable evidence points to the existence of pure amino acids as inner salts, that is, the point of equilibrium represented by eq. (1) lies far to the right. The physical properties, as



already mentioned, are those of highly polar species. However, since the charges on the inner salt molecules compensate each other, the molecules are not ions. Inner salts of this type are called *dipolar ions* or *zwitterions*. Salt formation by zwitterions follows the courses indicated by the reactions in eqs. (2) and (3). Note that an acid attacks the carboxylate group, a base the ammonio group.



The products of salt formation are ions, which are usually soluble in water and migrate in electrolytic cells. At some certain pH, the amino acid molecule is electrically neutral in solution. This pH is called the *isoelectric point*. At this pH the amino acid is least soluble and does not migrate in an electric current. On the other hand, aminodicarboxylic acids are acidic, and diaminomonomonocarboxylic acids, basic. Neutral solutions of these amino acids are mixtures of the free compounds with their salts, that is, buffer solutions. Therefore, ionic species are present, and the amino acid ions do migrate in an electrical current.

This behavior makes possible the separation of complex mixtures of amino acids by a process called *electrophoresis*. The solution at a desired pH is electrolyzed in a vessel of three chambers (Fig. 39-1) starting with the mixture in the middle chamber. Anions of more acidic amino acids migrate toward the anode, and appear in the chamber near this electrode; cations of more basic amino acids move to the opposite chamber. The

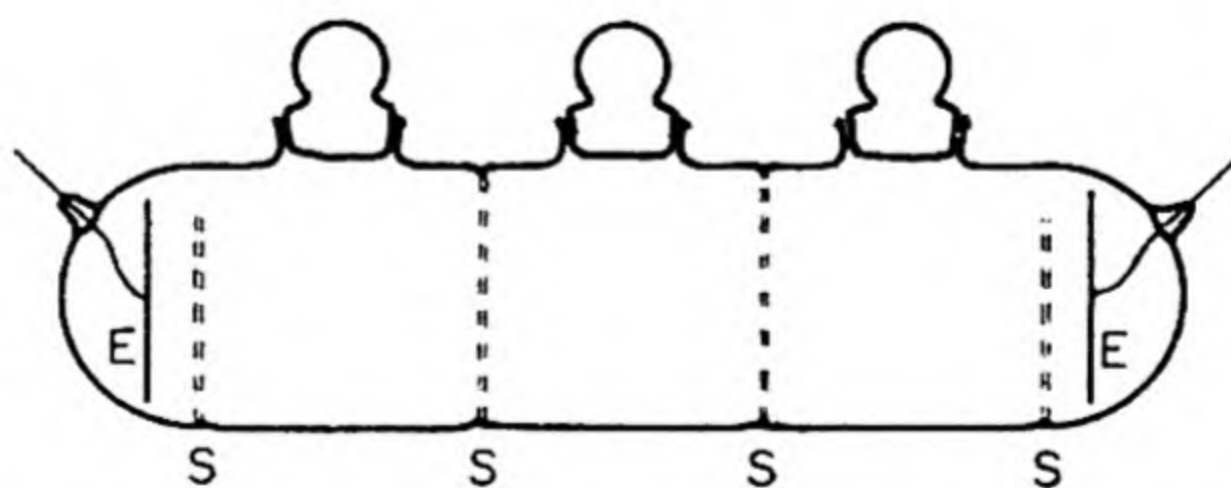
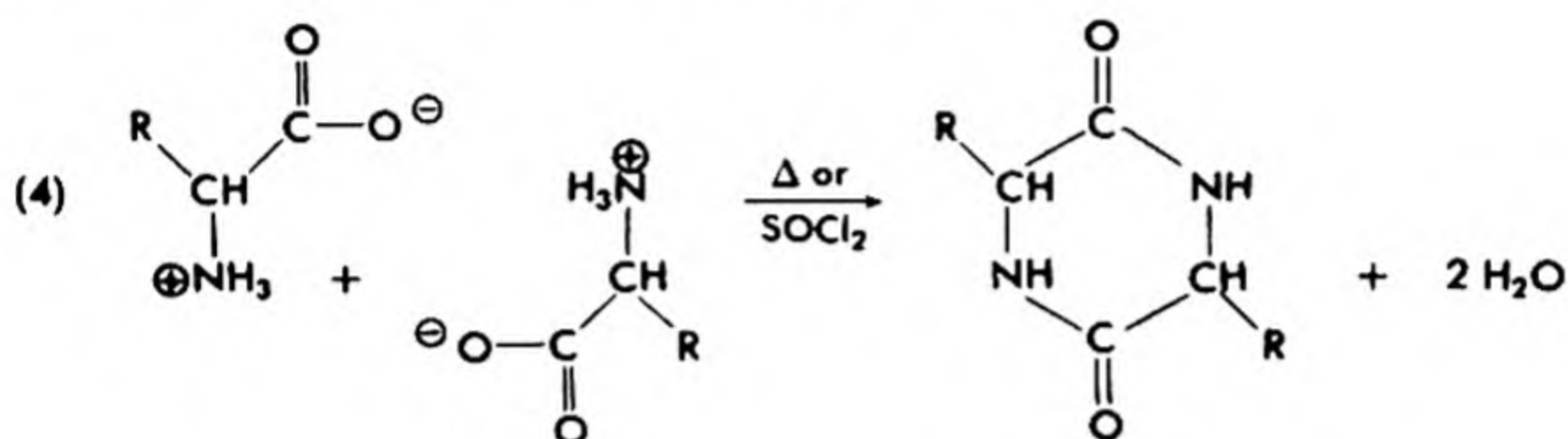


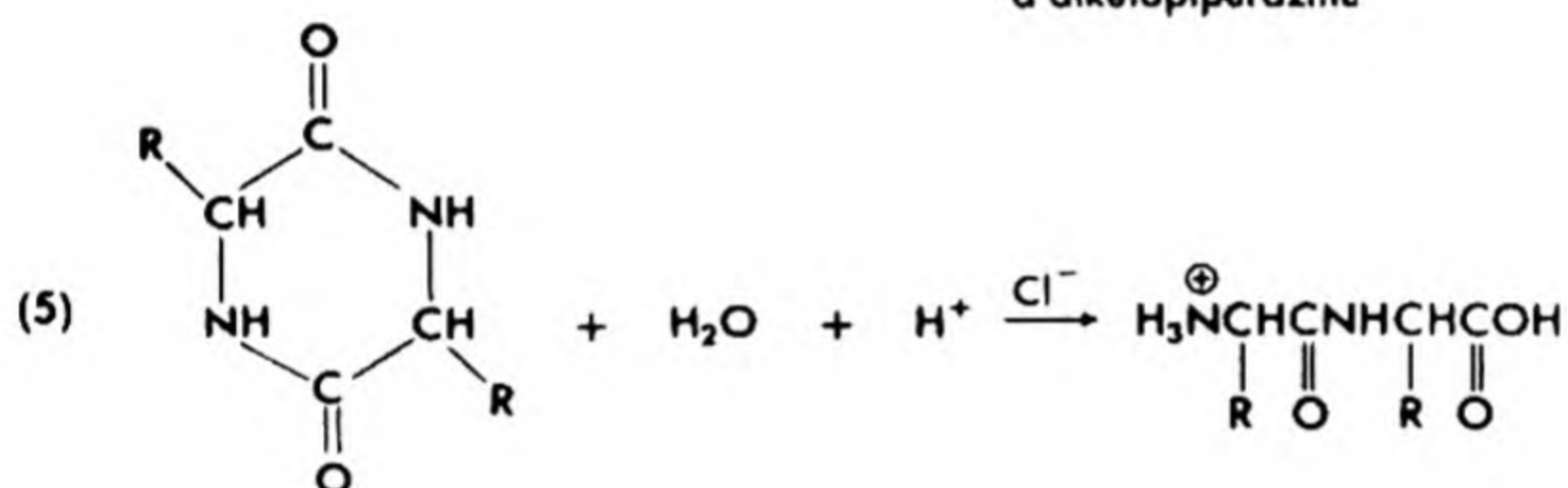
Fig. 39-1. Electrophoresis Cell (S) Sintered glass partitions, (E) Electrodes. Solution containing buffer and materials to be separated is placed in center chamber. Buffer solution is placed in each end chamber. Passage of electric current causes material in center chamber to migrate to right or left chamber.

process is stopped after a suitable extent of migration has occurred, but before much reaction occurs at the electrodes.

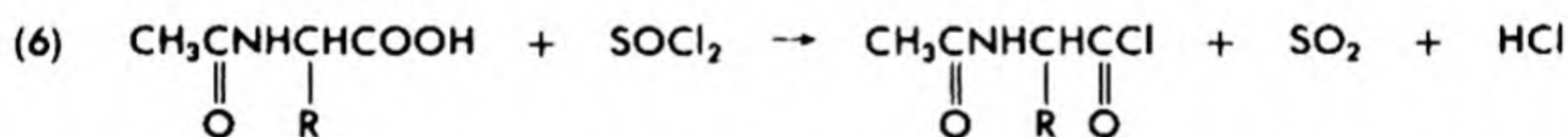
(2) *Reactions at the Carboxyl Groups.* Amino acids form esters and amides, just as simple carboxylic acids do. However, attempts to form anhydrides or acyl halides result in formation of cyclic diamides called diketopiperazines (eq. 4). These can be prepared in better yield by heating esters of the amino acids and are useful for the preparation of dipeptides by very carefully controlled hydrolysis (eq. 5).



a diketopiperazine

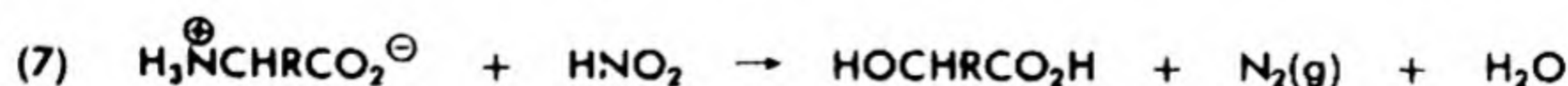


dipeptide hydrochloride



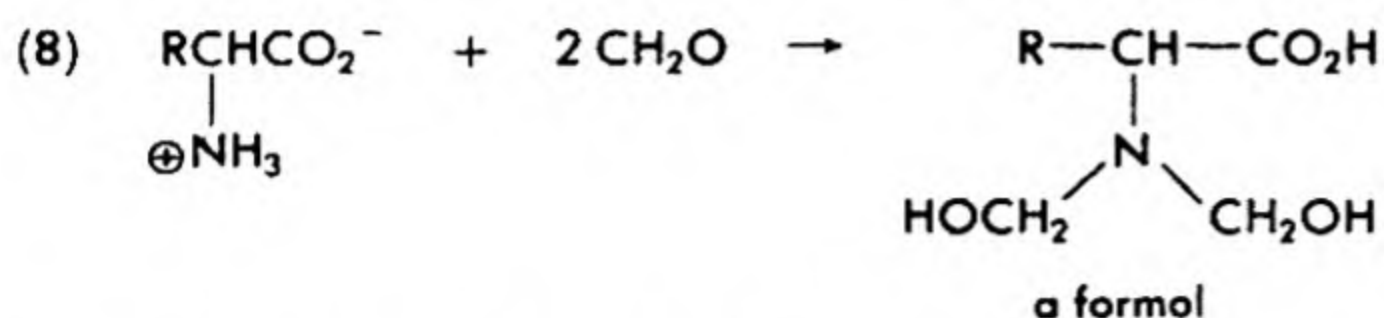
Acylated amino acids can readily be converted into the corresponding acyl halides (eq. 6), which are useful for the synthesis of peptides.

(3) *Reactions at the Amino Group.* All of the amino acids but the prolines exhibit reactions of primary amino groups, including acylation, nitrogen generation by nitrous acid, and reactions with aldehydes. The Van Slyke amino nitrogen determination (eq. 7) is an analytical tool much used in amino acid and protein chemistry. An analytical application of



the reaction with formaldehyde is also important. The *formol* produced has considerably reduced basic properties, hence can be titrated with

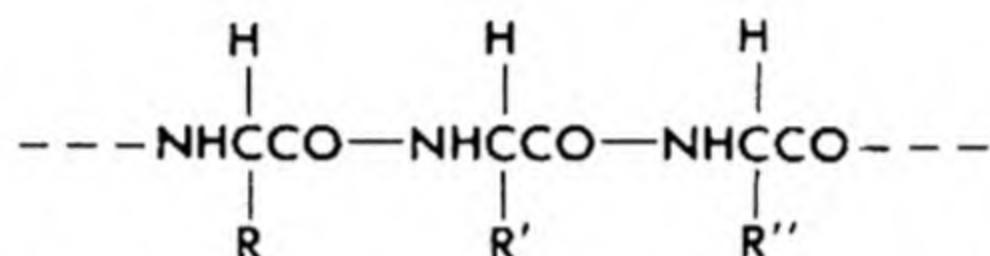
sodium hydroxide to determine free carboxyl group content (see eq. 8).



Condensed polymeric amide derivatives of amino acids are called *peptides*. Appropriate numerical prefixes indicate the number of amino acid units per molecule.

39-2 PROTEINS

Proteins are high-molecular-weight biological materials made up largely of alpha amino acid monomer units condensed into long polypeptide chains:



Although proteins differ greatly in their individual amino acid contents and in the orders in which the amino acids occur, the nitrogen content is so nearly constant (16%) that analysis for nitrogen is used as a basis for the estimation of the amount of protein in foods.

Molecular weights of proteins vary widely according to type and source, the extremes being 6,000 (insulin) and 20,000,000 (keratin).

A. Classification

Proteins are classified variously according to their constitution, physical nature, and solubility behavior. Those which yield only amino acids upon hydrolysis are called *simple proteins*. Those which give other types of products besides amino acids are *conjugated proteins*.

The groups in the original protein which engender the non-amino acid hydrolysis products are termed prosthetic groups (Gk., *pros* + *tithenai*, to place upon). Some conjugated proteins lose their prosthetic groups very readily; sometimes dialysis is sufficient to separate the amino acid chain (peptide chain) from the prosthetic groups. Consequently, it is not always clear when a native protein is simple and when it is conjugated. Add to this the fact that single small units from proteins of large molecular weight are mere traces in the midst of thousands of amino acid units, and the problem of classification of proteins becomes no small consideration. Some biochemists have raised the question whether any simple proteins exist in the living organism.

Derived proteins are substances of protein-like nature formed by denaturation or by partial hydrolysis of proteins. *Denaturation* is a mild

treatment which alters the physical properties, but not the chemical composition of a protein. This involves differences in coiling and internal hydrogen bonding.

The main classes of proteins and some examples of each are given in Table 39-2.

TABLE 39-2. Classification of Proteins

Name	Source	Characteristics
Albumins:		
Serum albumin	Blood serum	Soluble in water and dilute salt solutions, coagulated by heat
Ovalbumin	Egg white	
Myogen	Muscle	
Lactalbumin	Milk	
Globulins:		
Serum globulin	Blood serum	Insoluble in water, soluble in dilute salt solutions, coagulated by heat
Myosin	Muscle	
Thyroglobulin	Thyroid	
Glutelins:		
Glutenin	Wheat	Insoluble in water and dilute salts, soluble in dilute acids and bases
Oxyzenin	Rice	
Prolamines:		
Gliadin	Wheat	Like glutelins, except soluble in 70-80% ethanol
Hordein	Barley	
Zein	Corn	
Histones:		
Globin	Hemoglobin	Soluble in water and dilute acids, weakly basic, coagulate other proteins
Scombrone	Mackerel	
Thymus histone	Thymus	
Protamines:		
Salmin	Salmon sperm	Soluble in water and dilute acids, basic, not coagulated by heat, coagulate other proteins
Sturine	Sturgeon sperm	
Scombrine	Mackerel sperm	
Albuminoids:		
Keratin	Horn, hair, nails	Insoluble in reagents that do not decompose them
Fibroin	Silk	
Elastin	Ligaments	
Collagen	Hide, cartilage	

CONJUGATED PROTEINS

Name	Source	Prosthetic Groups
Nucleoproteins	Cell nuclei, genes, viruses	Nucleic acids (§42-3C)
Glycoproteins:		
Mucin	Saliva	Carbohydrates (Chapter 38)
Mucoids	Tendons, bone	

TABLE 39-2. Classification of Proteins (Cont.)

Name	Source	Prosthetic groups
CONJUGATED PROTEINS (CONT.)		
Phosphoproteins:		
Vitellin	Egg yolk	Phosphoric acid
Casein	Milk	
Chromoproteins:		
Hemoglobin	Erythrocytes	Porphyrins (§42-2)
Chlorophyll	Plant plastids	
Lipoproteins	Cell membranes	Fatty acids, lecithins (§40-1C, §40-4)
DERIVED PROTEINS		
Name	Treatment	
Denatured proteins	Heat, ultraviolet light, acid, alcohol, urea	
Coagulated proteins	Prolonged heat, alcohol	
Metaproteins	Nonhydrolytic treatment with acids or alkalies	
Proteans	Very slight hydrolysis by acids or alkalies	
Proteoses	Further hydrolysis. Water-soluble, not coagulable	
Peptones	Further hydrolysis. Not precipitated by saturated $(\text{NH}_4)_2\text{SO}_4$	

B. Physical Properties

An outstanding characteristic of proteins is their colloidal nature. Because of their many polar groups, proteins are hydrophilic, hence form aqueous gels with great ease. Protoplasm is, in fact, a sol-gel mixture surrounded by a somewhat stiffer gel that serves as a cell boundary or membrane.

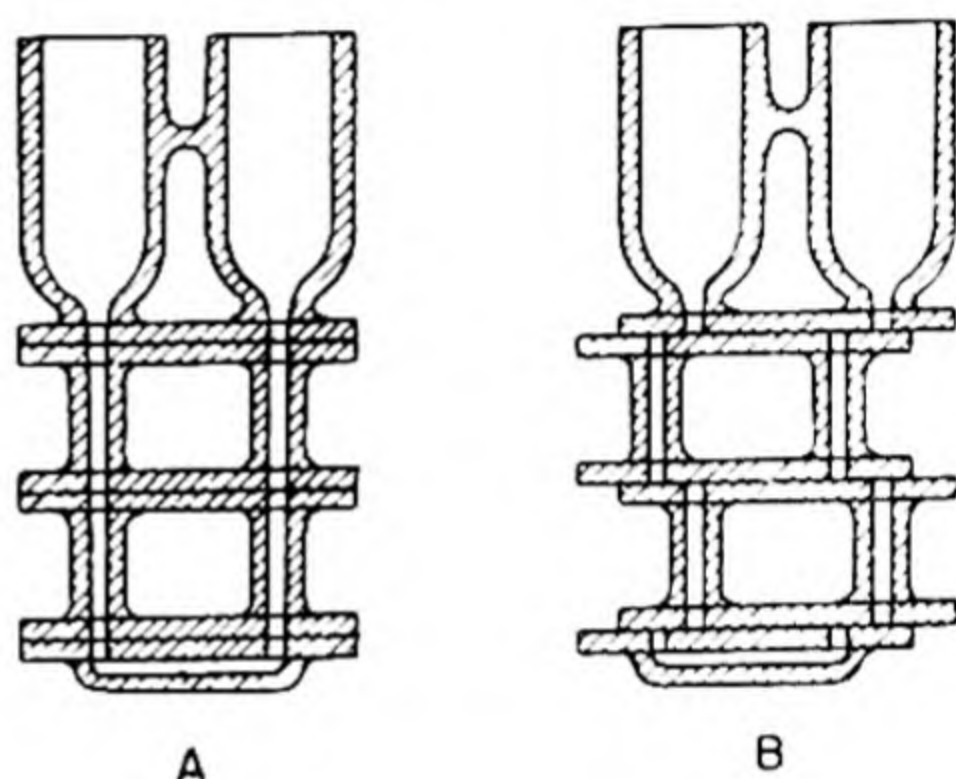
Working with proteins, then, is a matter of utilizing methods for dealing with colloids. One of the more familiar of these is dialysis. True solutes can be separated through suitable membranes from colloidal particles. Membranes of appropriate porosity can separate colloids of lower molecular weight from higher colloids. Dialysis is not, however, a general method for separating mixtures of colloids.

To separate proteins from each other requires methods capable of selection on the basis of molecular weights, densities, molecular shape, and ionic charge, if any. The ultracentrifuge utilizes the first three of these differences in properties. Protein solutions spun at rotations up to 80,000 rpm soon form layers based on molecular densities and molecular weights. Boundaries between the layers slowly move outward with time, and other boundaries may appear. If the separations are sharp enough, different layers can be collected as different fractions. Failure to form

more than one layer in the ultracentrifuge is used as a criterion of purity of a protein, since melting points are not meaningful.

A method which depends primarily upon ionic charge, and less directly upon the other properties, is electrophoresis. This operates in the same way for proteins as for amino acids (§39-1D(1)). The *Tiselius cell* (Fig. 39-2) was specially designed for the separation of proteins into fractions by electrophoresis. Again, formation of a single fraction in electrophoresis is a criterion of purity for a protein. If the protein sample can pass both the sedimentation test and the electrophoretic test, it is considered as pure as is possible to ascertain with present methods.

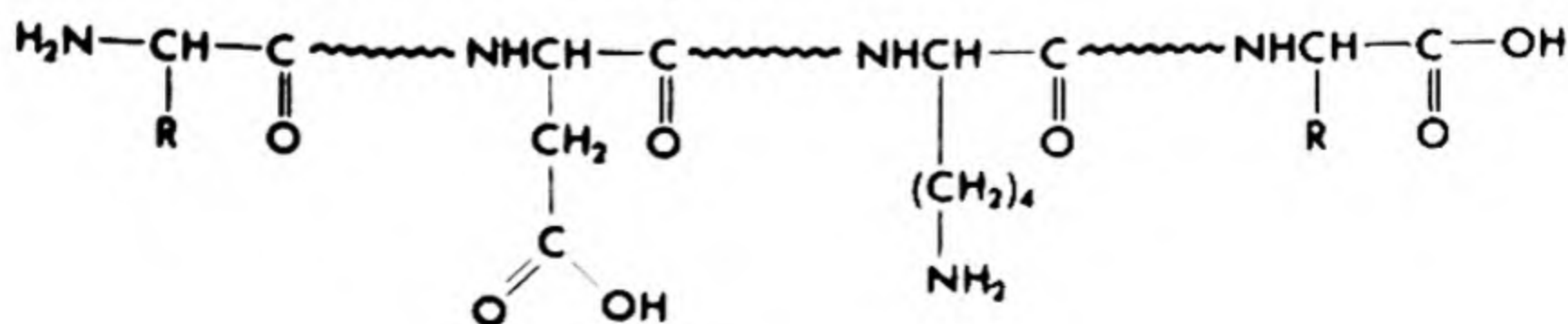
Fig. 39-2. Tiselius Cell in Cross Section. (A) Segments in line for electrophoresis, (B) Segments separated by sliding for isolation of sample fractions.



C. Chemical Properties

(1) *Acidity and Basicity.* Since proteins commonly have acidic and basic side chains derived from acidic amino acids and basic amino acids, as well as one basic and one acidic end group per molecule, proteins are amphoteric (see formula I). Proteins doubtless have forms corresponding to the amino acid zwitterions, but with their larger number of amino and carboxyl groups, these must have more than two charge centers.

As with amino acids, for each protein there exists some pH at which the number of positive and negative charges on the molecule is the same; hence the molecule is electrically neutral. This pH is the isoelectric point. At the isoelectric point the protein does not migrate in electrophoresis. At this pH, its solubility is a minimum. The isoelectric point for each protein or amino acid is characteristic.

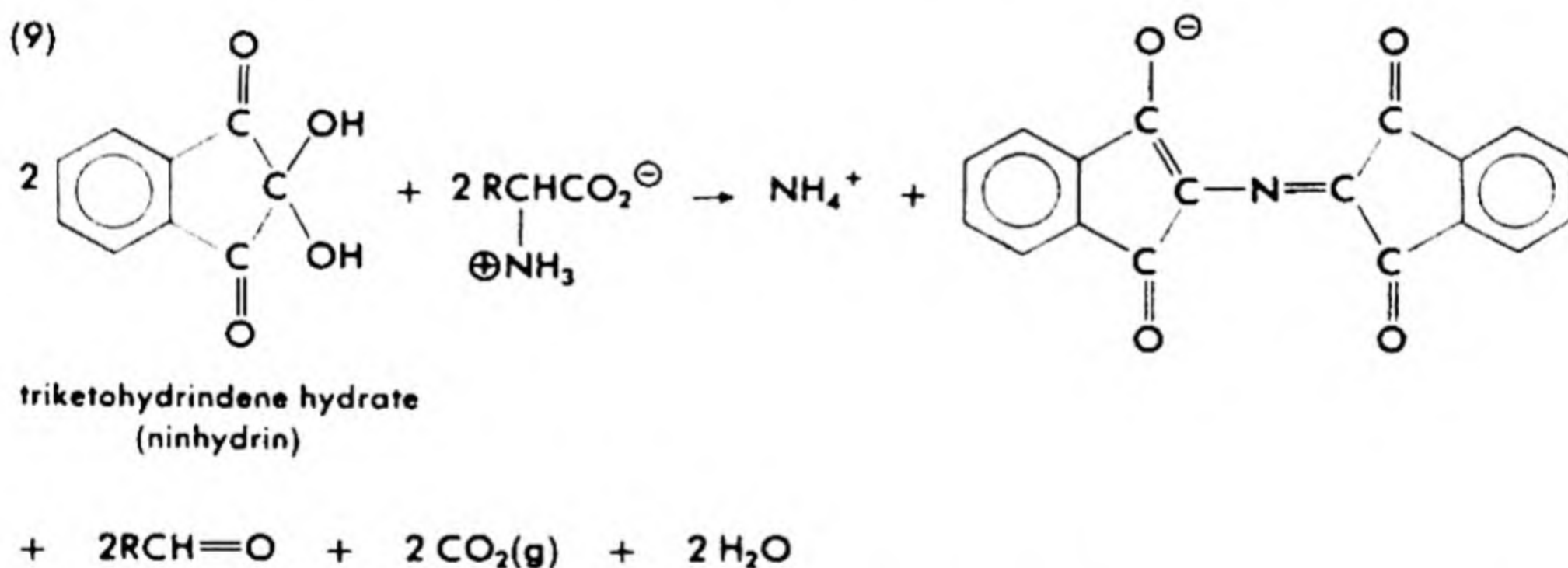


(2) *Hydrolysis.* The ease with which proteins are degraded by acids and by enzymes to various intermediates, and ultimately to amino acids, suggests that the long chains are connected by the amide linkage. This is confirmed by physical-chemical studies. Amides and proteins are cleaved by both mineral acids and bases with about the same ease. The fact that little or no racemization of amino acids occurs during acidic or enzymic hydrolysis supports the belief that asymmetric carbon atoms are not attacked during hydrolysis. On the other hand, sodium hydroxide does cause extensive racemization.

(3) *Analytical Reactions.* A number of chemical procedures have been developed to test for certain amino acid groups or to distinguish between protein derivatives.

The *ninhydrin reaction* (eq. 9) gives a pink color changing to intense blue when α -amino acids are present in neutral solution. Peptides yield no color change. In acidic solution, carbon dioxide is evolved and can give a quantitative estimate of free amino acids.

The *biuret reaction* is the formation of a cupric complex, blue-violet in color, between very dilute cupric sulfate and an alkaline solution of polypeptides or proteins. Amino acids and simple peptides give negative tests.



Phenolic groups in proteins respond to *Millon's reagent*, a complex mixture of mercuric nitrate and nitrite, nitric acid, and oxides of nitrogen made by dissolving mercury in concentrated nitric acid and diluting the product. Red colors are shown by tyrosine, iodogorgoic acid, thyroxine, and proteins containing units of these acids.

Another test which detects phenolic groups, as well as tryptophan units, is the *xanthoproteic test*. Concentrated nitric acid nitrates these readily substituted aromatic groups to give yellow polynitro aromatic groups. These are acidic and form deep orange anionic complexes when treated with ammonia.

D. Serological Assay

The intractability of proteins to present physical and chemical methods of separation implies that closely related proteins are practically indistinguishable by chemical and physical methods. More selective means of identification and differentiation of proteins depend upon biochemical processes in blood serum. If a foreign protein is injected into an animal's blood system, it sets up an irritation that causes the blood system to manufacture antibodies, which also are proteins and which precipitate the foreign protein. Blood serum taken from the sensitized animal will henceforth cause immediate coagulation of any sample of the same protein that caused formation of the antibodies. However, different proteins, either from the same source or from a similar source in a different species or subspecies, are not coagulated by the antibodies, showing that there is a definite, biologically detectable difference between the corresponding tissue proteins of different species.

Advantage is taken of the selectivity of the antibody reaction to distinguish between otherwise indistinguishable proteins and to identify samples of protein as being the same as others which produce the same antibody reaction.

E. Structure of Proteins

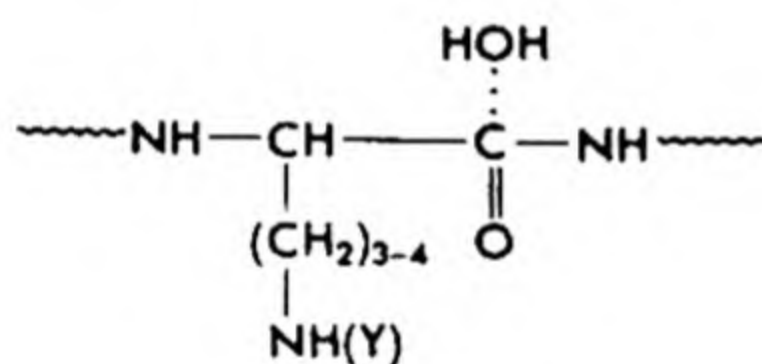
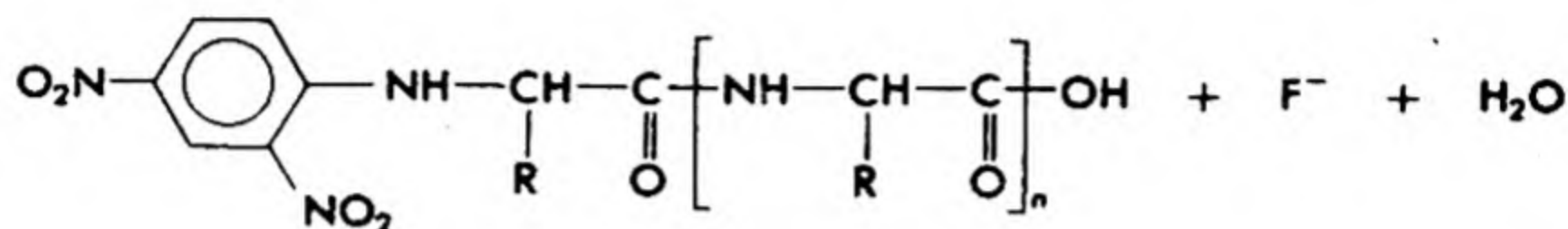
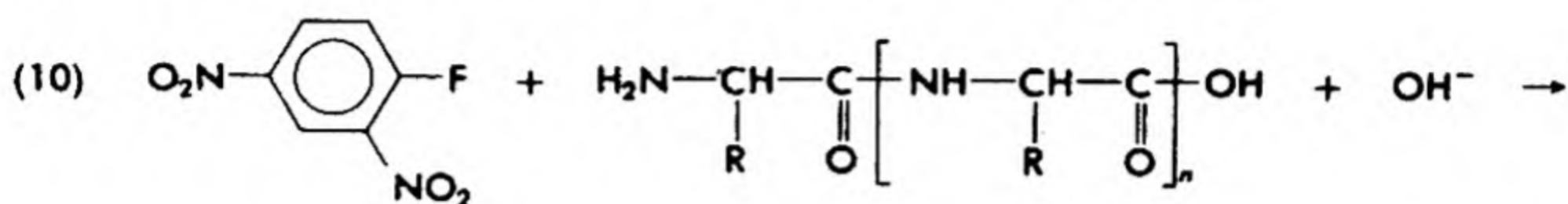
The difficulty of obtaining homogeneous protein samples and the large number of structural units making up proteins have been such strong deterrents to progress in this field that with but a few notable exceptions, only the gross features of protein structure have been established. Only recently have salients been pressed into the details of protein structure.

(1) *Degradation Studies.* Complete hydrolysis of proteins and analysis of the hydrolysates gives the ratio of amino acids present in the chain, but no clue as to their order. The first attempt to derive their order was the stepwise degradation of a protein chain one amino acid unit at a time by a process that utilized nine separate steps per unit. Understandably degradation studies never progressed very far under these conditions.

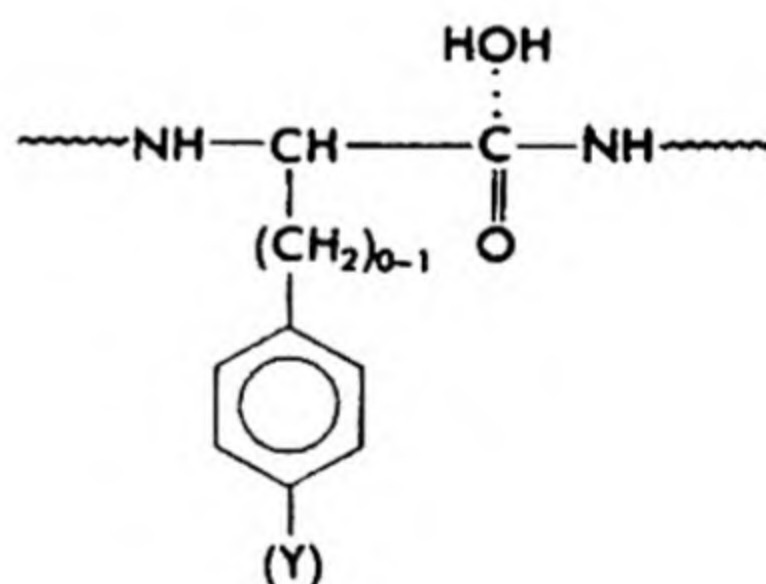
The first major breakthrough was the Nobel Prize-winning work of Frederick Sanger (1945-1950), which culminated in determination of the complete structure of insulin. Sanger used 2,4-dinitrofluorobenzene to label all free amino groups (eq. 10). Any compound which contains the resulting 2,4-dinitrophenylamino group is bright orange. Thus, the terminal amino group and all lysine units are labeled.

The next step was to break down the protein chain selectively by enzymic hydrolysis. Several modes of cleavage are possible depending on the specific enzyme (§39-3) used. A *carboxypeptidase* cleaves the free carboxyl end units, one at a time; careful timing makes possible degrada-

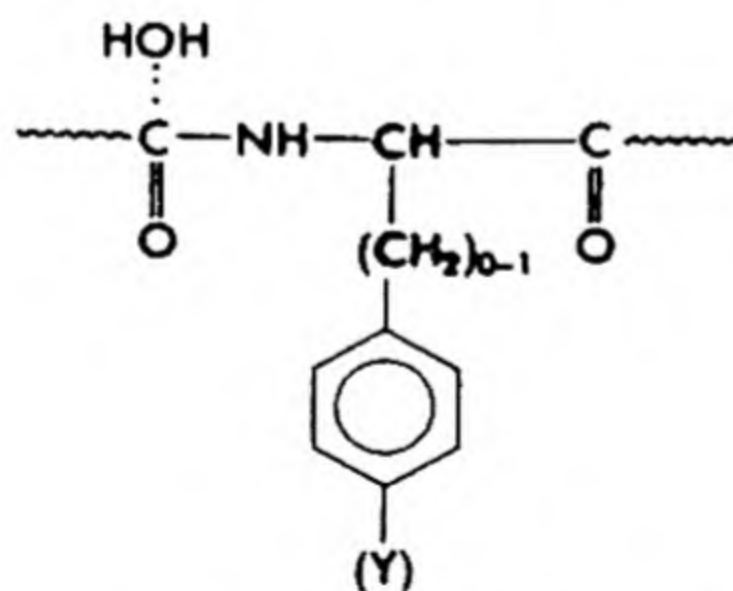
tion of just one unit. Still more useful are *endopeptidases*, which cleave the chain along its length *at certain specific linkages*. Thus, trypsin breaks a polypeptide at each lysyl or arginyl unit, II; chymotrypsin at each aromatic unit, III, and pepsin at each peptidyl aromatic unit, IV (provided the unit to the left of the aromatic unit is not basic).



II trypsin catalysis $\text{Y} = \text{H}$ or $\begin{array}{c} \text{NH} \\ \parallel \\ \text{C} \\ \parallel \\ \text{NH}_2 \end{array}$



III chymotrypsin catalysis
 $\text{Y} = \text{H}$ or OH

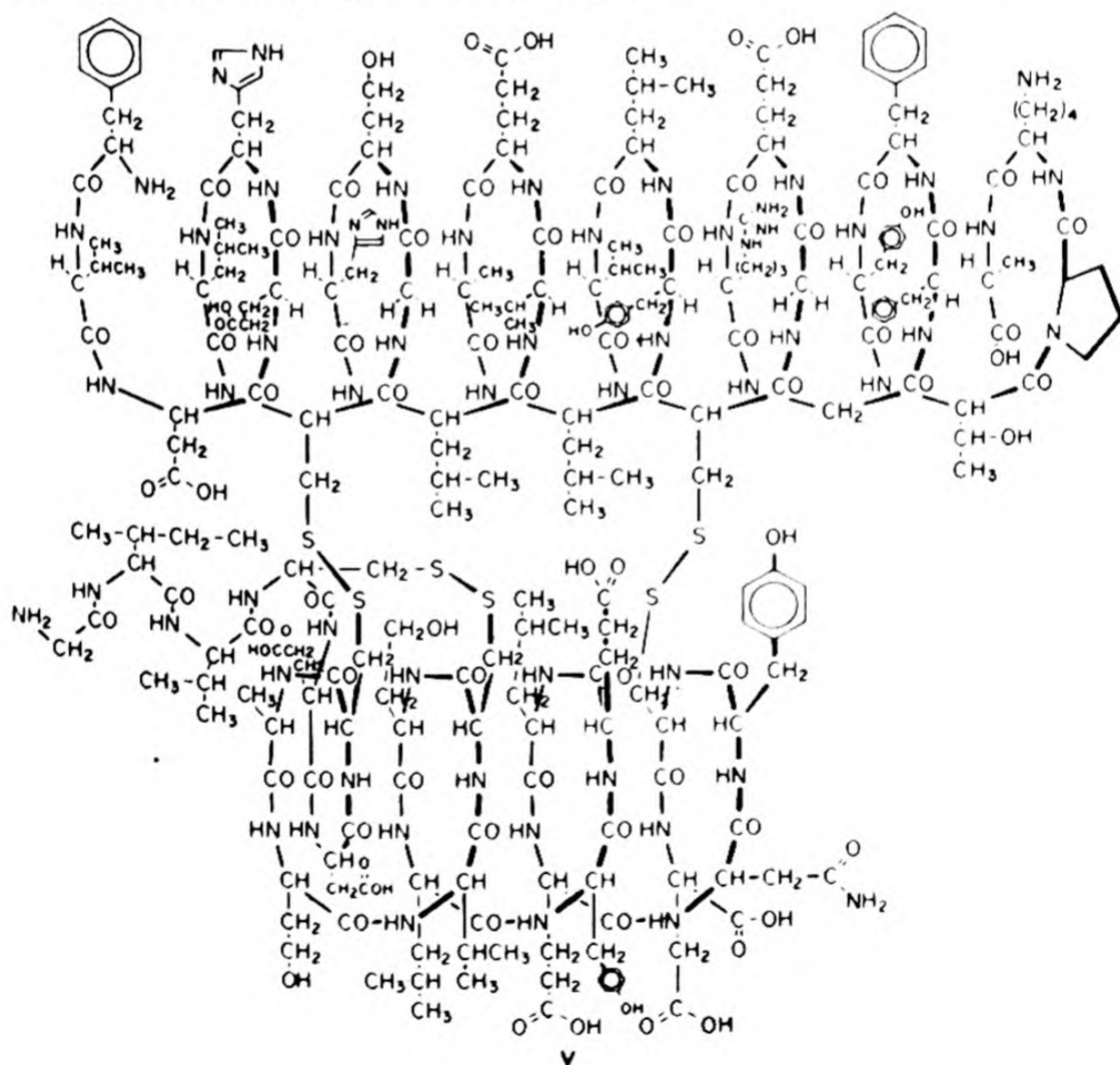


IV pepsin catalysis $\text{Y} = \text{H}$ or OH

The hydrolysis of the protein chain by a given enzyme or combination of enzymes thus breaks the polypeptide chain down to a number of shorter peptides. These are then separated by *chromatography*, a method

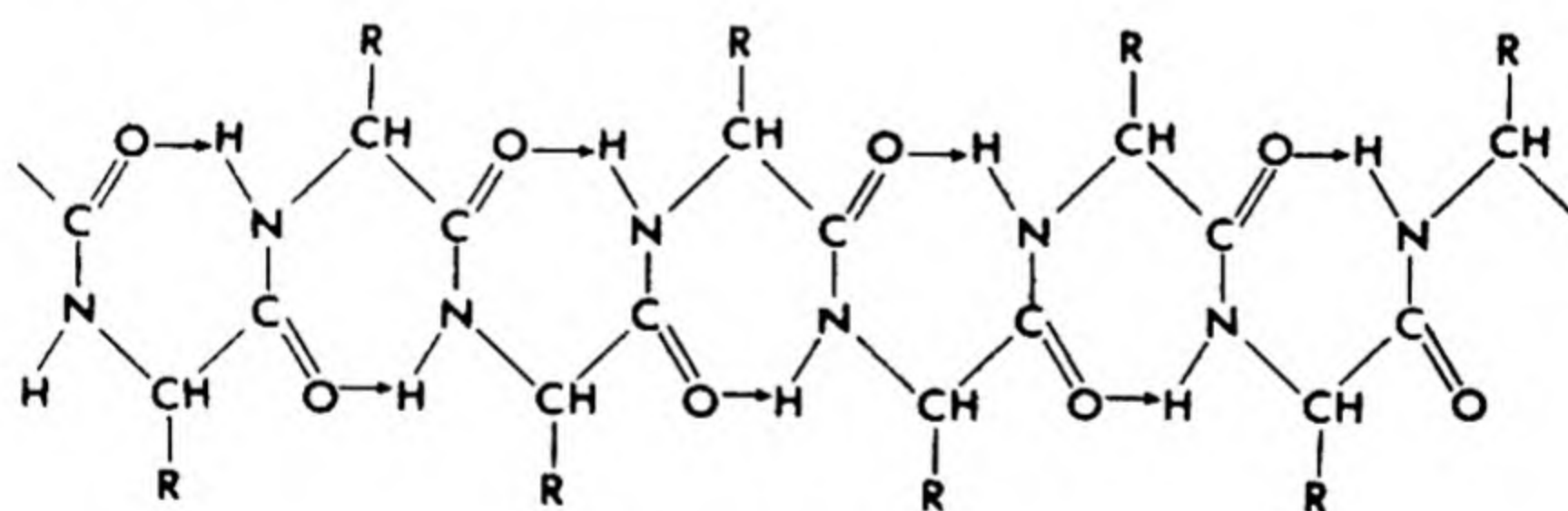
which utilizes selective adsorption on a solid as a solution is passed through a packed column. The terminal group and all former lysyl-containing groups appear as orange bands; all others are colorless and must be detected by analytical reactions (§39-2C(3)). These separated, shorter peptides can now be degraded stepwise with the carboxypeptidases to determine their amino acid sequence. In general, the original protein is broken down to units of one to four amino acids, so that the determination of sequence upon these is much less formidable than a similar determination upon the original protein.

Insulin was shown to consist of two polypeptide chains connected by disulfide units in cystine, with one glycyl amino-end unit and one phenylalanyl amino-end unit. Identification of the various hydrolysis products which resulted from different modes of hydrolysis presented a sort of crossword puzzle for sequence-fitting to correspond with the known number of amino acid units in each chain. The result of completing this scientific crossword puzzle was the complete structure of insulin, V.



Sanger's work on insulin was paralleled by utilization of similar methods on two polypeptide hormones, oxytocin and vasopressin (§43-2). These smaller polypeptides are cyclic, hence have no end groups. Vincent du Vigneaud (Nobel laureate, 1955) and his students not only determined the structures of these hormones, but also synthesized them. These are the first naturally occurring polypeptides to have been synthesized. Insulin has now been synthesized (P. G. Katsoyannis and co-workers, Pittsburgh, Pa. and H. Zahn and co-workers, Aachen, Germany).

Determination of the order and number of amino acid units in a protein molecule is just the beginning of the battle, however. The behavior of many proteins when heated, treated with alcohol, or otherwise denatured indicates that the change is not in destruction of peptide linkages, but in the physical orientation of the groups in the molecule. Many proteins have coiled molecules. Diffraction studies have confirmed in some proteins the probability of the 2_7 or α -II fold. The folds are linked between the carbonyl atoms and the amino hydrogen atoms of alternate amino acid units by hydrogen bonds. The designation 2_7 fold comes from the two amino acids in each loop, which form a seven-membered ring. Most proteins have a spiral, N_{13} fold (Fig. 39-3). X-ray diffraction studies established that long regions of the N_{13} spiral occur even in the structure of myoglobin, a muscular globulin.



2_7 or α -II fold

(2) *Syntheses.* The orderly organic chemist does not feel comfortable about the proposed structure of a compound until it has been defended not only by degradation, but also by synthesis from smaller units. In protein chemistry, this means putting amino acid units together to form a long protein chain. Because of the sketchy knowledge available of the order of arrangement of amino acids in most proteins, it has proved impracticable to attempt complete synthesis of most natural proteins. The probability that, by randomly putting together all the amino acids present, in the proportions they exist, to form a specific protein is vanishingly small, about one in 10^{470} even in the relatively simple case of a polypeptide made up of five each of twenty different amino acid units.

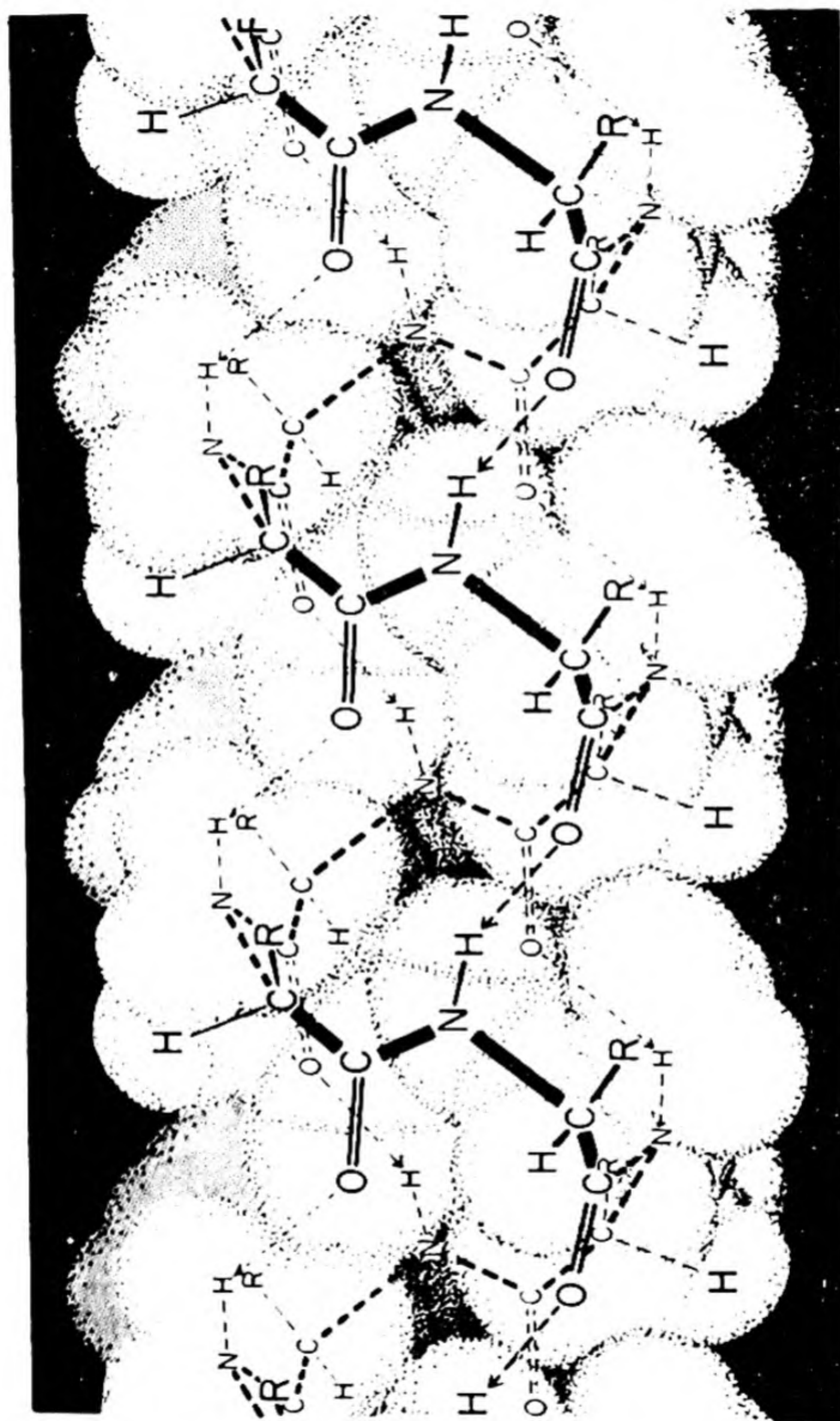
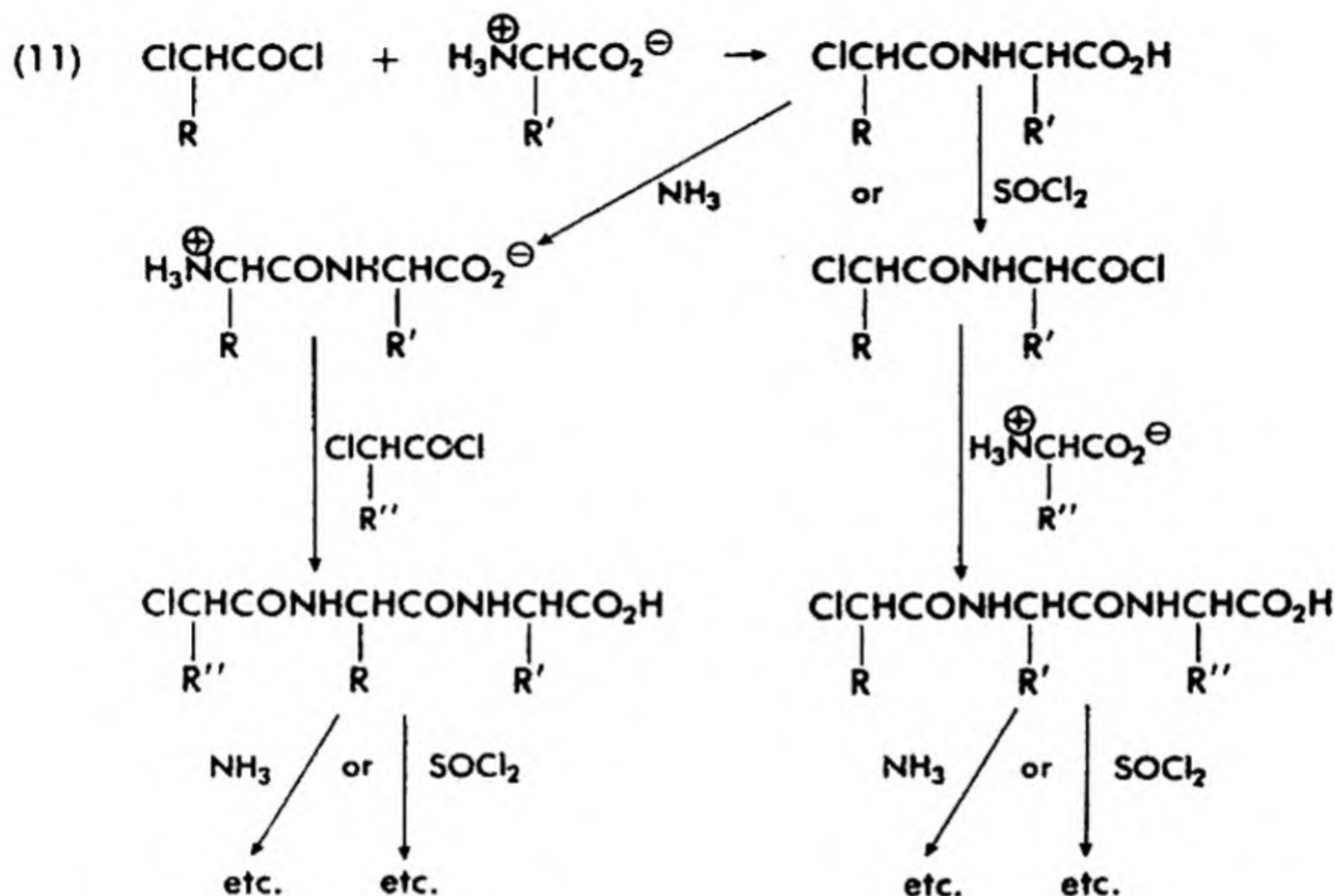


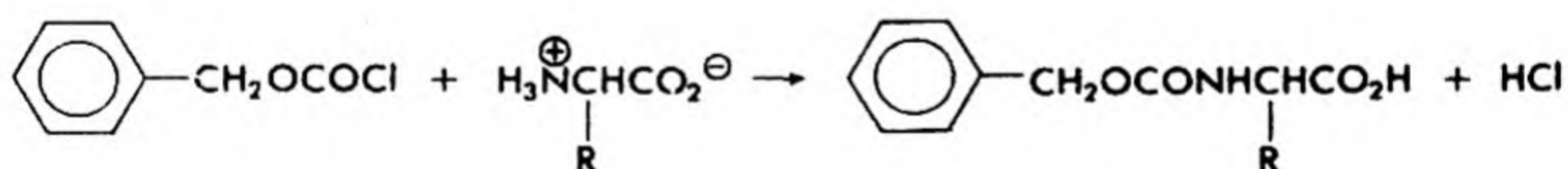
Fig. 39-3. Segment of Polypeptide Chain in N_{13} Fold.

One scheme used to prepare polypeptides is shown in outline (11). After the desired number of amino acid units has been added to the polypeptide, the final replacement of the terminal chlorine atom by an amino group is accomplished. A polypeptide synthesized in this manner by Emil Fischer with eighteen amino acid units, molecular weight 1212, had distinctly protein-like characteristics.



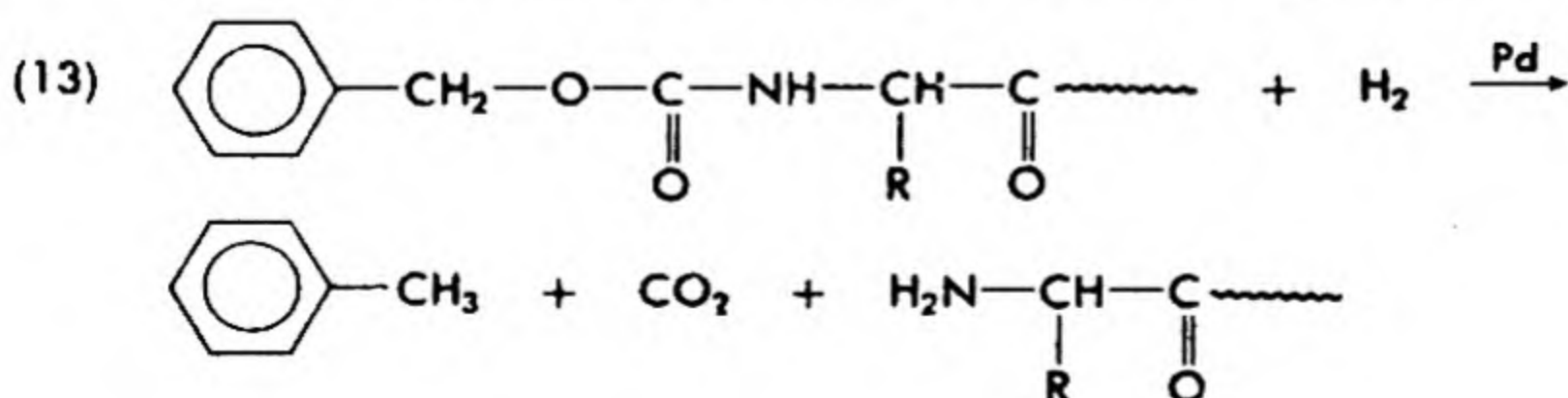
A number of schemes have been used to protect the terminal amino group or carboxyl group of a peptide or amino acid undergoing incorporation into a polypeptide chain. The carbobenzyloxy group, introduced as in eq. (12), is widely used for protecting amino groups.

(12)



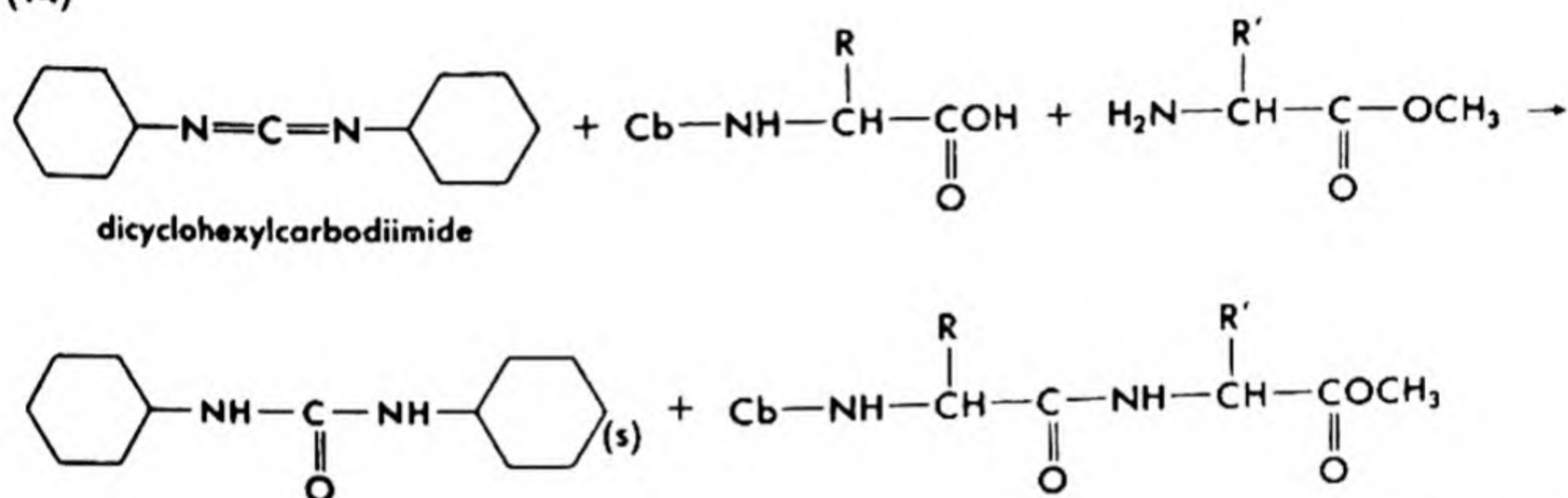
since it can be removed by mild reduction (eq. 13) without endangering the peptide linkages.

Several methods have been used for connecting the carbobenzyloxy (Cb)



protected amino acid to the amino end of the next unit. Originally, the Cb-amino acid was converted to its acyl halide, which then formed the peptide link as any such amide synthesis is performed. The carboxyl end of the product could be converted to its acyl halide, and the sequence repeated as often as desired. However, a number of the side chains of amino acids are more susceptible to SOCl_2 than the carboxyl group, so that other methods were sought. An obvious approach is to form the peptide bond by dehydration. A dehydrating agent that is well suited to this method is *N,N'*-dicyclohexylcarbodiimide, which forms a precipitate of *N,N'*-dicyclohexylurea in a suitable solvent such as tetrahydrofuran or acetonitrile.

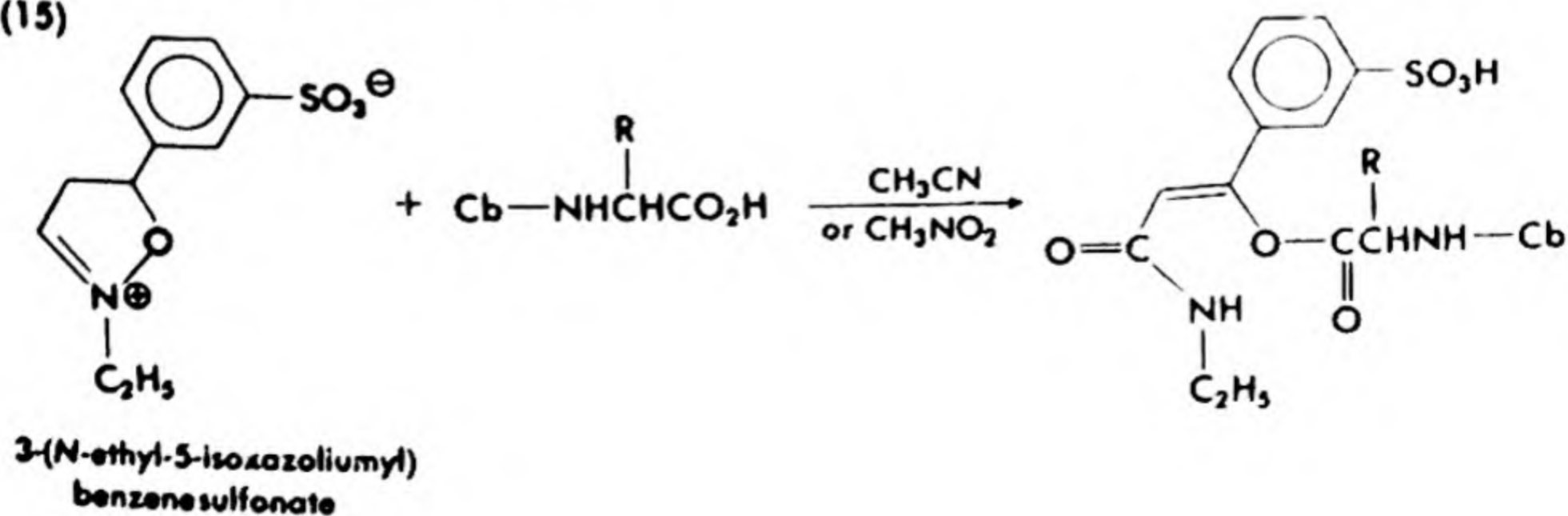
(14)

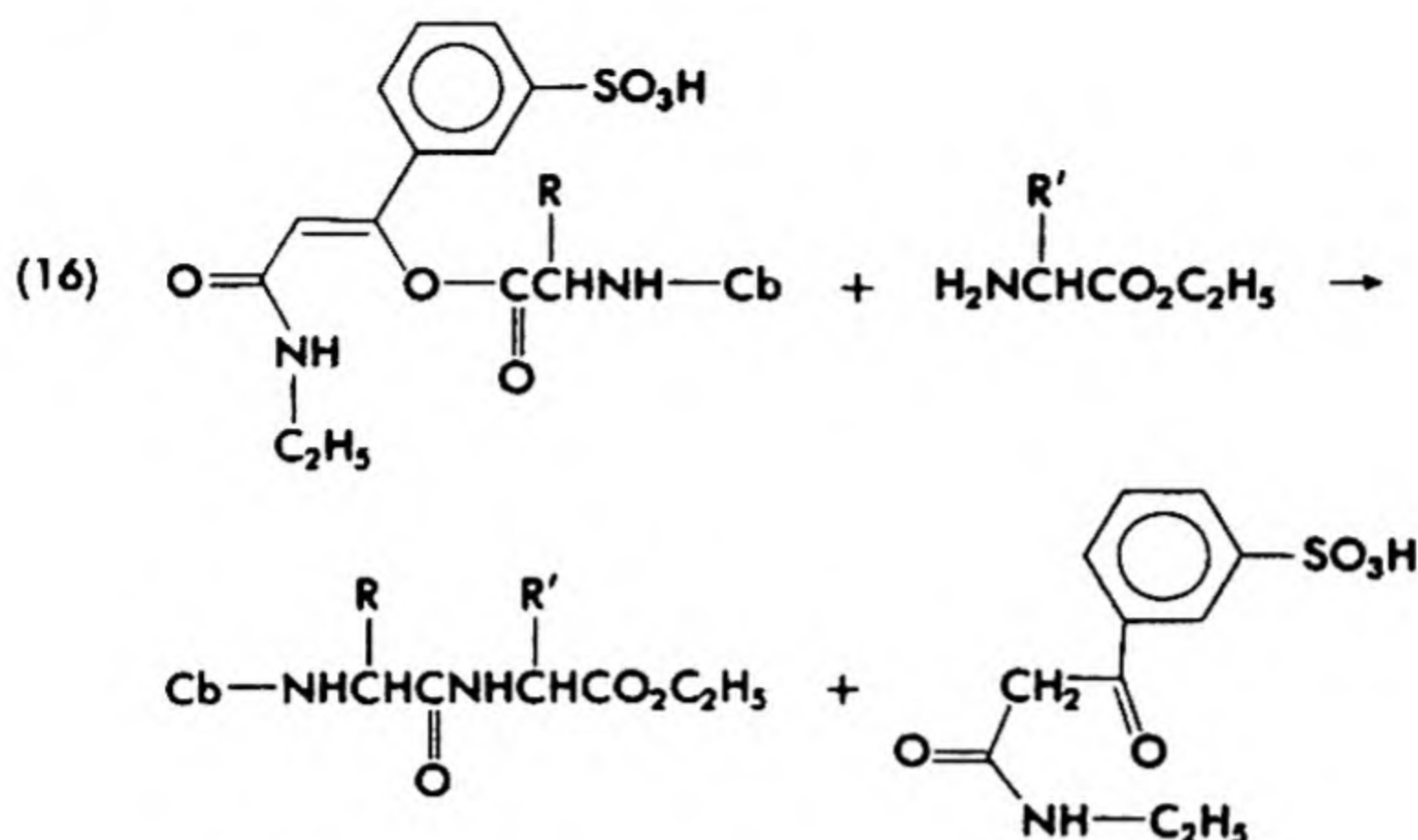


This same dehydrating agent can be used to promote formation of specially active esters, such as the *p*-nitrophenyl ester of an amino acid, which then can form the peptide bond by reaction between the ester group and an amino group.

R. B. Woodward (who with his students has synthesized a large number of complex natural products) devised a somewhat exotic, but very effective method for forming peptide bonds (1961). His reagent, 3-(*N*-ethyl-5-isoxazoliumyl)benzenesulfonate, forms a reactive ester with the protected amino acid or peptide. The final by-product, unlike the end-protected peptide, is water soluble. Professor Woodward was the Nobel Prize winner in chemistry in 1965.

(15)





39-3 ENZYMES

Enzymes are biological catalysts. Most are made up of two parts, a polypeptide, called the *apoenzyme*, and a prosthetic group, called a *co-enzyme*. The coenzyme is usually very loosely attached to the apoenzyme to form a complex called the *holoenzyme*.

The coenzyme is the part of the holoenzyme that brings about chemical reactions. The apoenzyme promotes the reaction and determines what type of substance is acted upon. The specificity of an enzyme is due to the uniqueness of fit between the apoenzyme and the material undergoing reaction. The latter is called the *substrate*.

A. Mechanism of Enzyme Actions

Since both the coenzyme and the apoenzyme must act upon a substrate simultaneously, there must be one or more active centers on both portions of the holoenzyme with which the substrate forms a temporary association. After formation of an enzyme-substrate complex, the substrate is vulnerable to attack by some specific substance from the environment or some reactive group on the coenzyme itself.

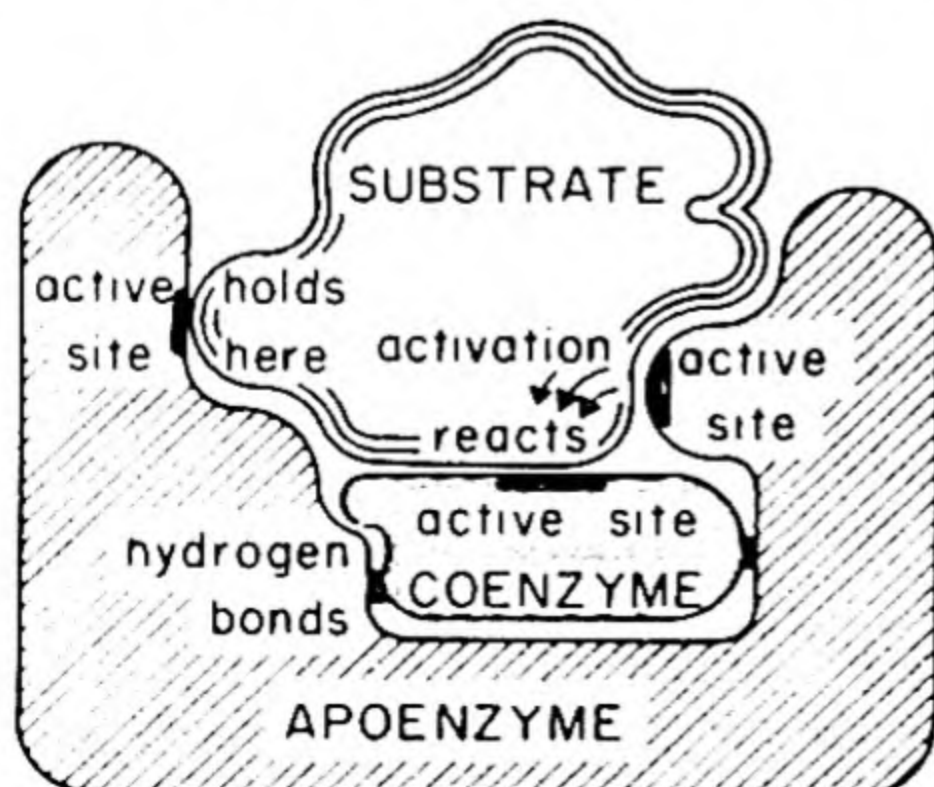
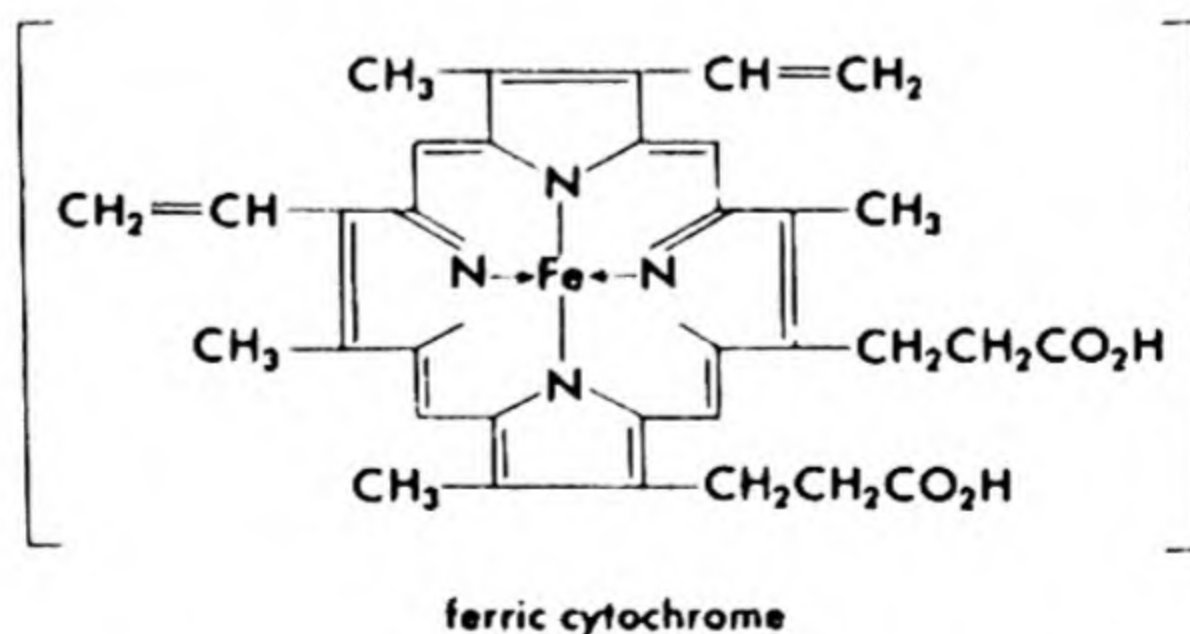
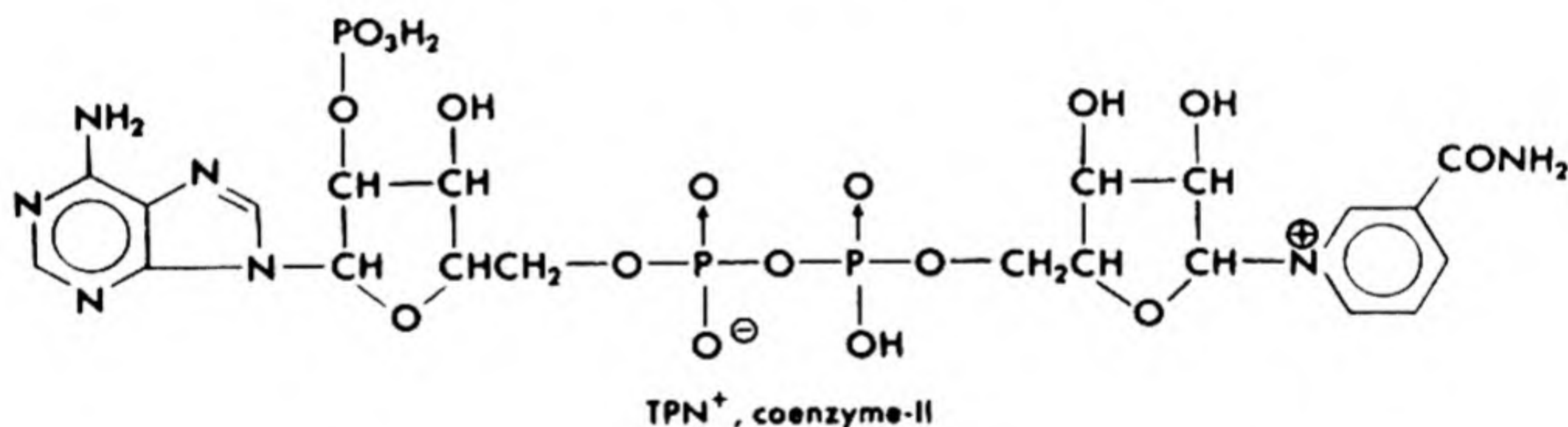
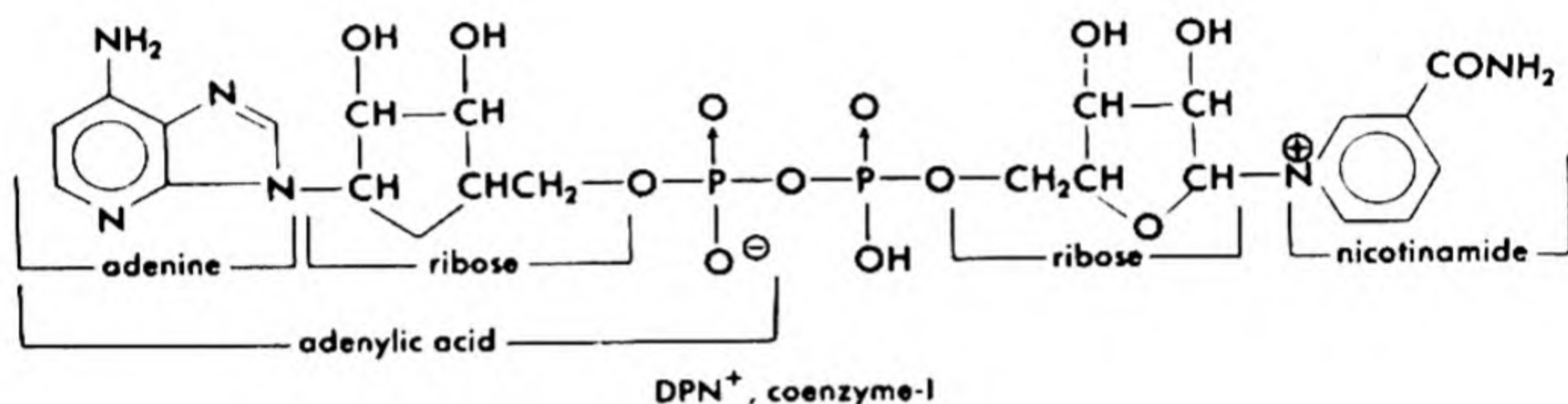


Fig. 39-4. Diagrammatic Representation of Enzyme-Substrate Complex.

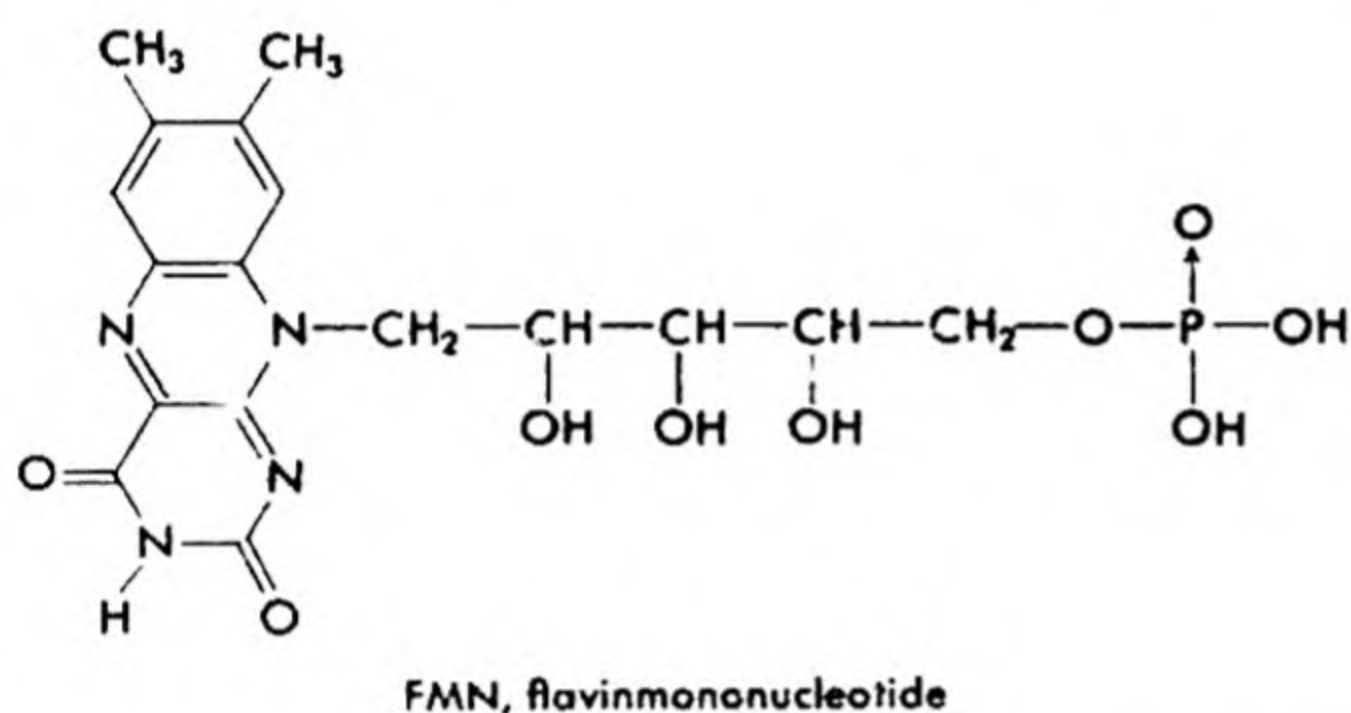
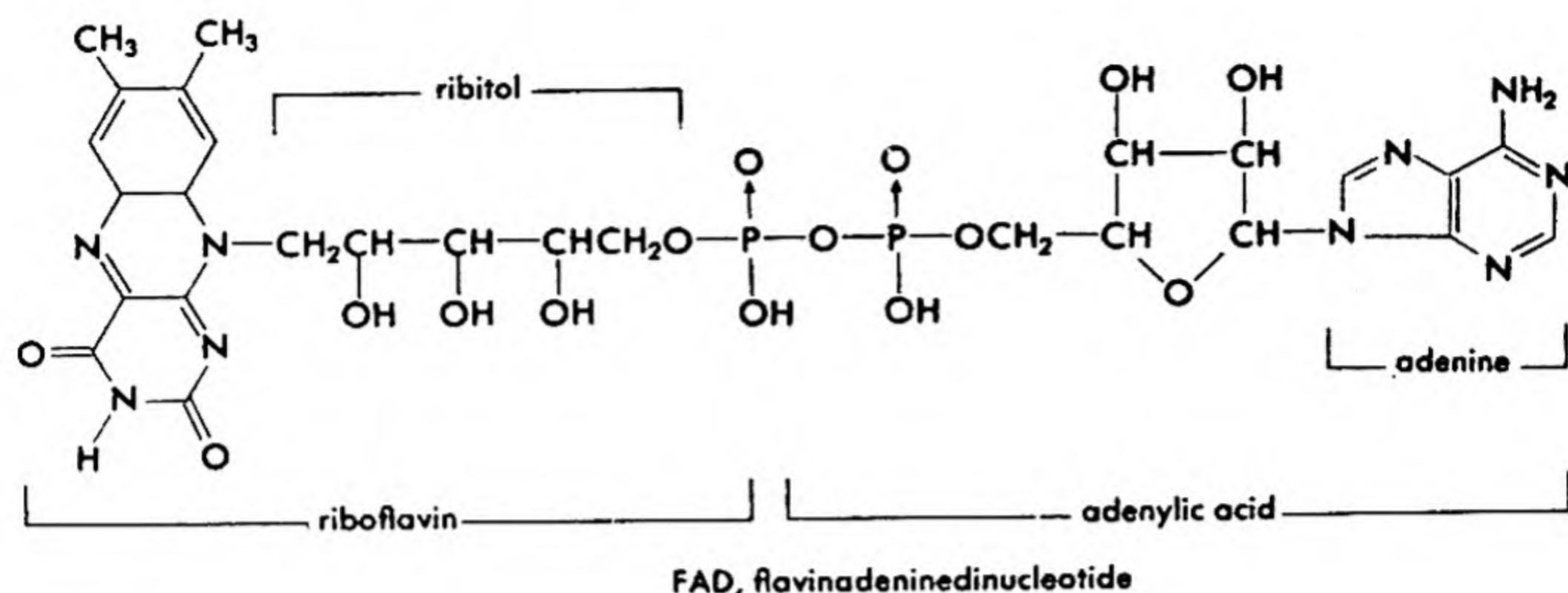
The specificity of the enzyme is determined by the particular spacing of groups on the apoenzyme. A coenzyme can act with a number of different apoenzymes, but in each case upon a different substrate (see Fig. 39-4).

B. Some Important Coenzymes

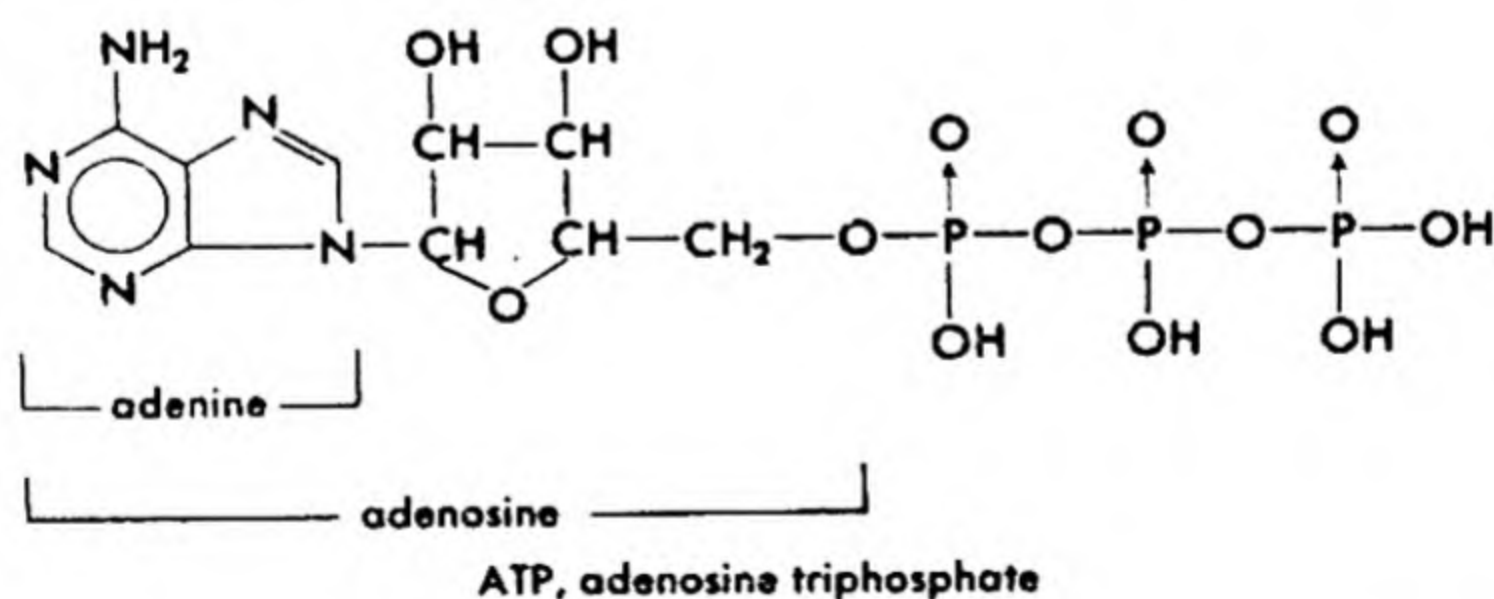
Some of the more important oxidizing coenzymes are coenzyme-I, or DPN^+ , coenzyme-II, or TPN^+ , and ferric cytochrome. The full names of the first two enzymes are diphosphopyridine nucleotide and triphosphopyridine nucleotide. Both contain units of nicotinamide, one of the B vitamins.



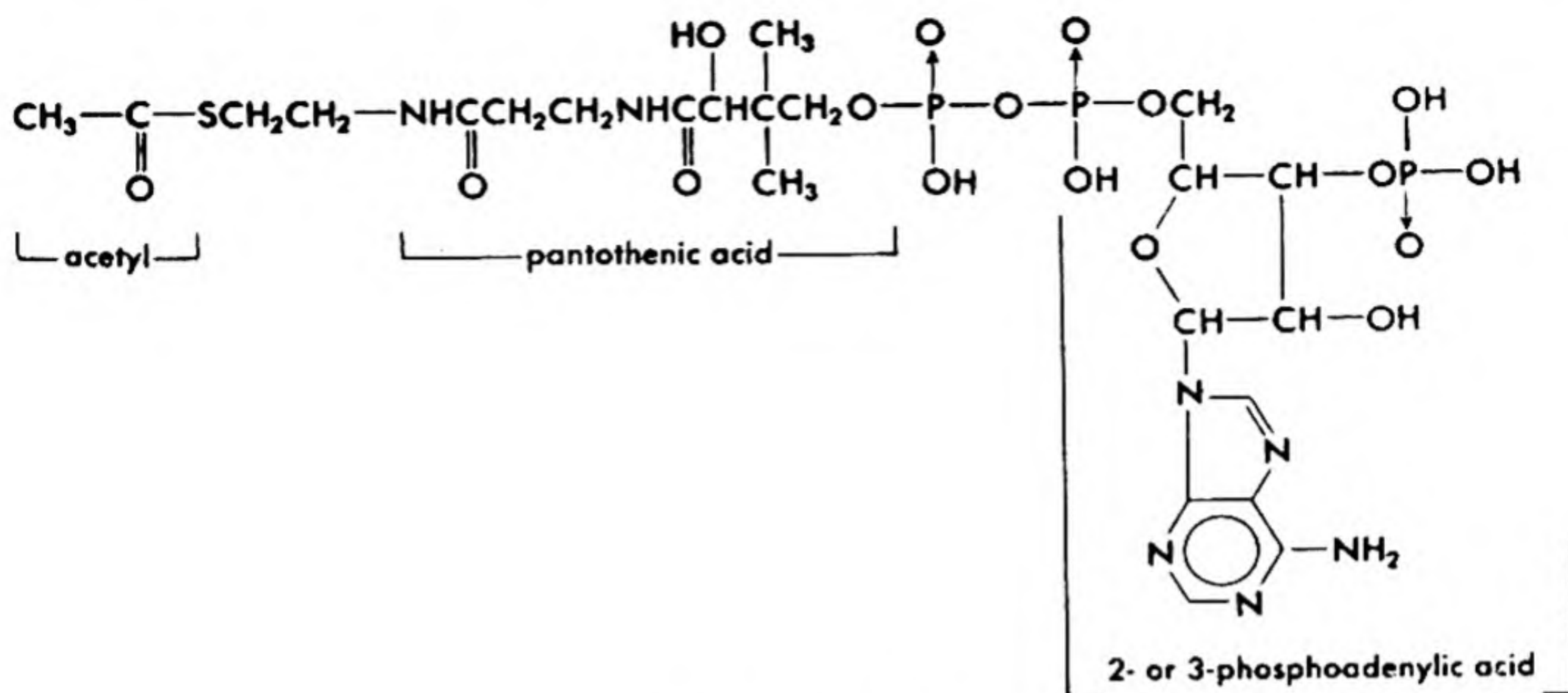
Other important oxidizing coenzymes are FAD (flavinadeninedinucleotide) and FMN (flavinmononucleotide). These coenzymes have units of riboflavin, vitamin B_2 .



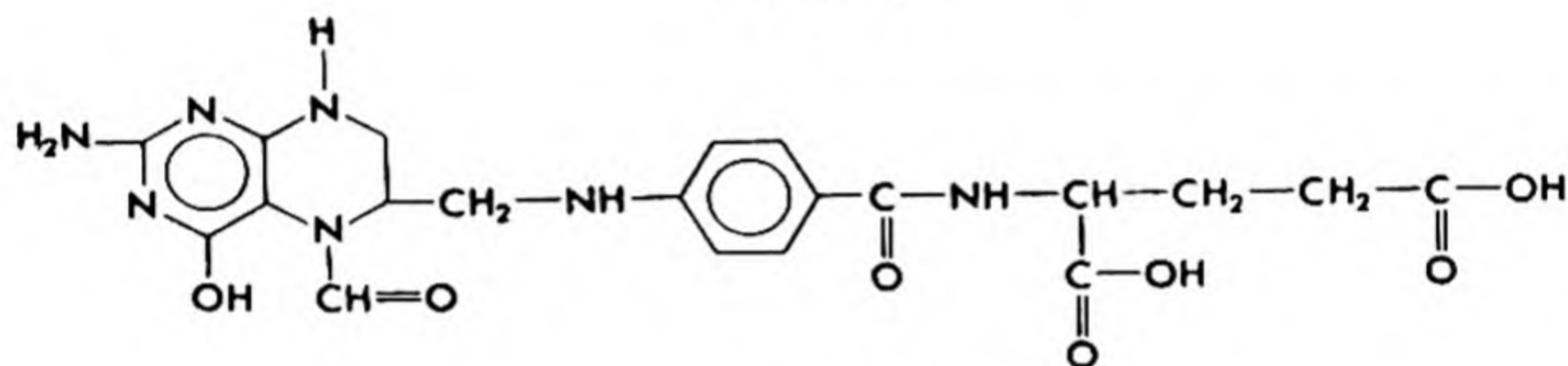
ATP (adenosine triphosphate) is the important energy-transfer co-enzyme. ADP and AMP are adenosine phosphorylated with diphosphate and monophosphate, respectively.



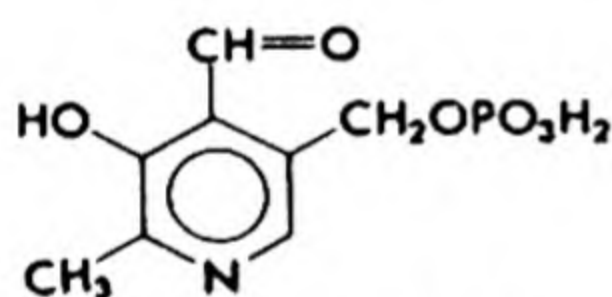
Two coenzymes are important because of their role in the synthesis of many of the compounds the body makes for itself. One is "active acetate," or acetyl coenzyme-A. The other is "active formate," or folic acid. Acetyl coenzyme-A has a unit of pantothenic acid, another B vitamin. Folic acid, less the formyl group, is folic acid, still another B vitamin.



acetyl coenzyme A



folic acid



pyridoxal phosphate

A coenzyme important to the metabolism of proteins and amino acids is pyridoxal phosphate, the phosphate of the aldehyde related to pyridoxine, or vitamin B₆.

Studies of the biological mechanisms of reactions mediated by enzymes are fascinating ones of considerable current interest. Students are referred to books on this topic by Kosower and by Ingraham.

SUPPLEMENTARY READINGS

Dixon, M., and E. C. Webb, *Enzymes*, Academic Press, New York, 1958.

Greenstein, J. P., and M. Winitz, *Chemistry of the Amino Acids*, Wiley, New York, 1961.

Ingraham, L. L., *Biochemical Mechanisms*, Wiley, New York, 1962.

Kendrew, J. C., "The Three Dimensional Structure of a Protein Molecule," *Sci. Am.*, 205 No. 6, 96-110 (December, 1961).

Kosower, E. M., *Molecular Biochemistry*, McGraw-Hill, New York, 1962.

Pauling, L., R. B. Corey, and R. Hayward, "The Structure of Protein Molecules," *Sci. Am.*, **191** No. 1, 51-59 (July, 1954),

Pfeiffer, J. E.,* "Enzymes," *Sci. Am.*, **179** No. 6, 28-39 (December, 1948).

Thompson, E. O. P.,* "The Insulin Molecule," *Sci. Am.*, **192** No. 5, 36-41 (May, 1955).

QUESTIONS AND PROBLEMS

1. Show by use of formulas or diagrams accompanied by verbal explanation that you know what is meant by the following terms.

- | | |
|-------------------------|-----------------------|
| a. peptide linkage | h. simple protein |
| b. zwitterion | i. conjugated protein |
| c. essential amino acid | j. diketopiperazine |
| d. prosthetic group | k. polypeptide |
| e. serological assay | l. apoenzyme |
| f. N_{13} fold | m. coenzyme |
| g. substrate | n. holoenzyme |

2. Describe the use of electrophoresis in amino acid and protein chemistry.

3. How could the isoelectric point of a protein be determined by electrophoresis? by solubility?

4. Explain why an enzyme is very specific and selective.

5. What class of foodstuffs is represented in many coenzymes? Of what class of foodstuff are apoenzymes made?

6. Write equations for the reactions that occur between the reagents below. Use structural formulas for organic compounds.

- | | |
|---------------------------------|--|
| a. glycine + hydrochloric acid | e. lysine + sodium nitrite + hydrochloric acid |
| b. L-alanine + sodium hydroxide | f. L-alanine + methyl alcohol + sulfuric acid |
| c. valine + thionyl chloride | g. glycine + chloroacetyl chloride |
| d. isoleucine + formaldehyde | |

7. Show how the compounds below can be prepared from the indicated starting materials. Use structural formulas for organic compounds. Specify essential conditions and reagents.

- | | |
|--|---|
| a. DL-alanine from ethyl alcohol | d. serine from ethyl acetate and formaldehyde |
| b. glycylvalylalanine from the necessary acid derivatives | e. phenylalanine from cinnamic acid |
| c. isoleucine from ethyl malonate and the necessary alkyl halide | |

8. Show how the compounds below can be distinguished by simple chemical tests. Describe the observed differences in behavior.

*Readings by Pfeiffer and Thompson are included in a reprint compilation entitled *Physics and Chemistry of Life*, Simon and Schuster, New York, 1955.

- | | |
|---|---------------------------|
| a. glycylglycine and glycylglycyl-glycylglycine | c. alanine and gelatin |
| b. lysine and leucine | d. casein and dextrin |
| | e. tryptophan and proline |

9. A tripeptide isolated from a protein hydrolysate was treated with 2,4-dinitrofluorobenzene. The product was treated with aqueous carboxypeptidase, after which methionine was isolated. The dinitrophenylated dipeptide remaining was hydrolyzed and gave *N*-2,4-dinitrophenylalanine and 6-(2,4-dinitrophenylamino)-2-aminohexanoic acid. Write the structure of the original tripeptide.

10. A polypeptide containing one unit each of glycine, alanine, phenylalanine, and tyrosine and two units each of glutamic acid and serine was obtained from a protein. Partial hydrolysis of the polypeptide gave fragments which were identified as serylserine, glycylglutamic acid, glutamylphenylalanylglycine, glutamyl-tyrosylserine, and alanylglutamylphenylalanine. Reconstruct the order of amino acids in the original polypeptide.

40

Fats, Oils, Waxes, and Detergents

40-1 LIPIDS

When biological tissues are extracted with organic solvents such as ether, chloroform, or benzene, a portion of the material dissolves. The components of the soluble material are called *lipids*. Several classes of lipids are quite unrelated in structure, properties, biosynthesis, and biological degradation.

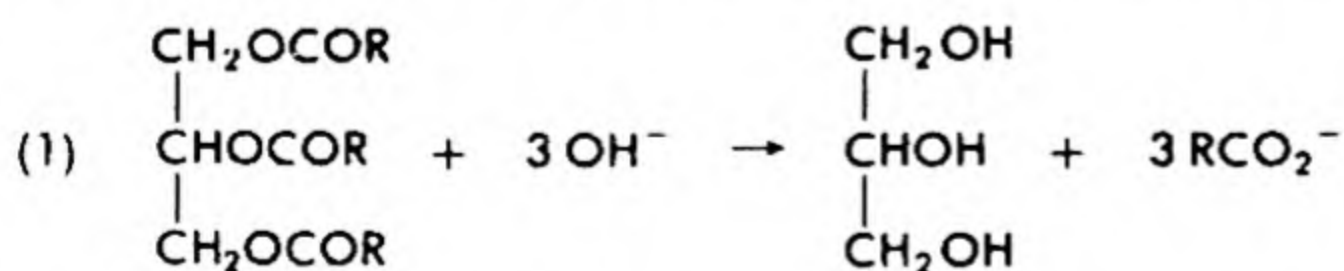
The simplest lipids are the fats, oils, and waxes. (The term "oil" here refers to vegetable oils and not to petroleum fractions.) Since these are also commercially and biochemically important, and since their properties are typical of many types of lipids, the bulk of this chapter is concerned with the simple lipids.

A. Physical Properties of Fats and Oils

The simple lipids are either relatively nonvolatile, viscous liquids or waxy, low-melting solids. As indicated above, these are soluble in organic solvents and insoluble in aqueous media.

B. Chemical Properties

(1) *Hydrolysis and Saponification Number*. Fats and oils are esters of organic monocarboxylic acids and of glycerol and are hydrolyzable either by aqueous acid or by alkali (eq. 1). The latter method is termed *saponifi-*



cation, because it produces soap (L., *sapo*, soap). Saponification of a fat produces soluble salts of fatty acids and soluble glycerol. Waxes are esters of long chain aliphatic acids with long chain aliphatic alcohols, so that alkaline hydrolysis gives a soluble soap, but the alcohol is insoluble.

The alkali equivalent of a fat is expressed as its *saponification number*. This is defined as the number of milligrams of potassium hydroxide which

react with 1 g. of fat. Typical saponification numbers of representative fats are given in Table 40-1. The variation in saponification numbers of fats from a given source reveals the heterogenous nature of the fat. Several different acyl groups are present in differing proportions in fats even from the same source.

(2) *Reactions Involving Unsaturation.* Both saturated and unsaturated even-numbered carboxylic acids are derived from fats and oils. In vegetable oils, unsaturated acyl groups predominate. The fats of fish are somewhat more saturated, and in some animal fats saturated acyl groups predominate. The degree of unsaturation of a fat can be measured by halogenation. To avoid substitution, which may occur to some extent with bromine, the less reactive halogenating agents, iodine monobromide or iodine monochloride, are used.

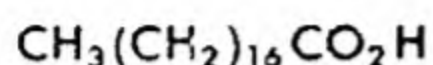
TABLE 40-1. Analytical Values of Representative Fats

Fat	Saponification Number	Iodine Number	Average Double Bonds per Molecule
Human fat	193-200	57-73	2.2
Beef tallow	190-200	35-48	1.4
Butter	210-241	22-38	0.9
Lard	190-203	47-77	2.1
Cod liver oil	171-189	137-166	5.6
Menhaden oil	189-193	140-185	5.6
Coconut oil	246-265	6-10	0.2
Cottonseed oil	189-198	99-114	3.6
Soy bean oil	189-197	120-141	4.5
Linseed oil	188-196	155-205	6.2
Tung oil	189-197	160-175	5.8

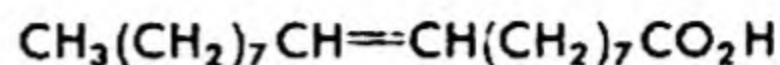
The quantitative estimate of unsaturation of a fat is expressed as its *iodine number*. This is the number of grams of halogen, as iodine, taken up by 100 g. of fat. The iodine number depends on the average number of double bonds per molecule and the average molecular weight of the fat. Typical values for representative fats are given in Table 40-1.

Like other unsaturated compounds, fats can be hydrogenated. The melting point of a fat is related to its degree of saturation. From Table 40-1 it is apparent that vegetable oils and fish oils are quite unsaturated, whereas solid animal fats are composed in large part of saturated compounds. Partial hydrogenation, therefore, converts liquid fats into solid fats suitable for conventional baking and frying methods. Unfortunately, this also decreases the amount of essential dietary fatty acid units avail-

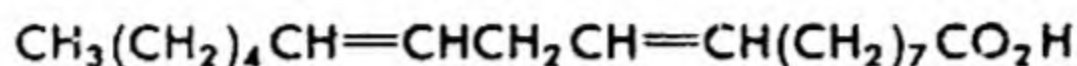
able in the fat. The essential acids are linoleic, linolenic, and arachidonic acids. Tentative evidence has been obtained which links insufficient essential unsaturated fatty acid residues in diet to cardiovascular diseases.



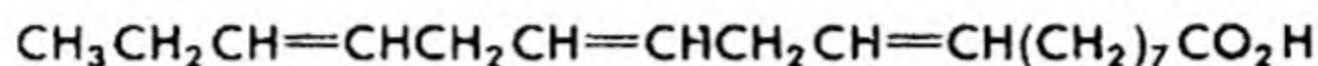
stearic acid



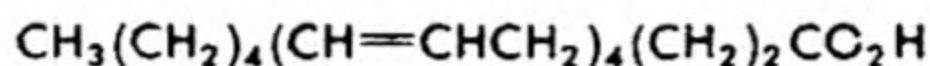
oleic acid



linoleic acid



linolenic acid



arachidonic acid

Air oxidation of multiple bonds is an important, if slow, reaction of unsaturated fats. The formation of low molecular weight carboxylic acids caused by oxidation of multiple bonds is responsible for the development of rancidity in unsaturated fats. This process can be inhibited by adding antioxidants to the fats. Such compounds as α -tocopherol (vitamin E), gallic acid, and ascorbic acid are suitable antioxidants.

Air-initiated polymerization is responsible for the setting of "drying" oils. These are oils with high proportions of polyunsaturated fatty acid units, such as linoleic acid, linolenic acid, and eleostearic acid. Commercially useful drying oils are soy bean oil, linseed oil, tung oil, and menhaden oil. These are oils with especially high iodine numbers (Table 40-1). The oils are heated to convert the double bond systems from isolated to conjugated. "Drying" of these oils is due to the formation of tough, hard, cross-linked polymer films plasticized by the small amounts of saturated fats present. The polymerization is promoted by the presence of certain metal ions, such as lead. The course of polymerization is obscure, but undoubtedly involves the formation of hydroperoxides at the allylic carbon-hydrogen bonds and cross-linking through allylic free radical intermediates.

C. Structure of Fats.

The first step in analyzing the structures of lipids is the procurement of relatively homogeneous specimens. Methods involving high temperatures, which are likely to change the structures of lipids by transesterification and multiple bond migration or isomerization, must be avoided. Consequently, crystallization methods have proved to be most fruitful to such structural analyses.

Hydrolysis of a sample converts 1 mole of fat to 1 mole of glycerol and 3 moles of a mixture of fatty acids. The fatty acids are converted to

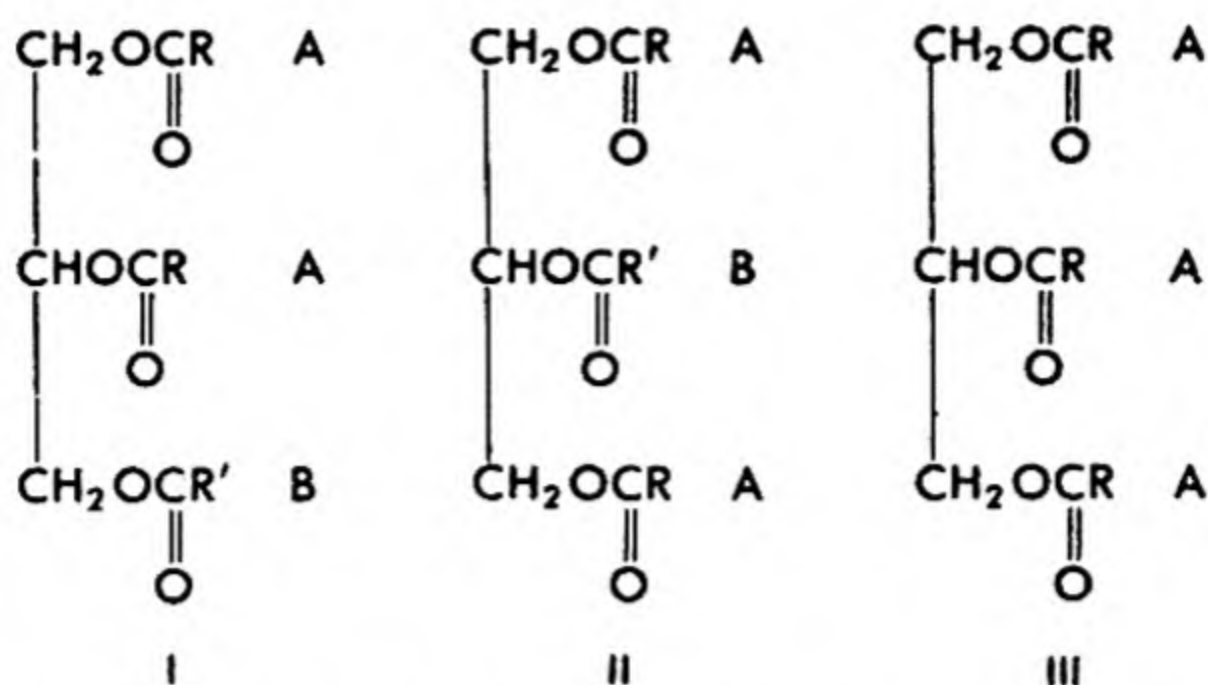
methyl esters, which are readily separated by vapor-phase chromatography. Some typical compositions of representative fats are given in Table 40-2. Determination of the nature and percentage of the individual triglycerides of which the original fat is composed is a formidable prob-

TABLE 40-2. Fatty Acid Components of Representative Fats

Acids from Fat		Per Cent in Each of Following Fats									
Common Name	IUPAC Name	Beef Tallow	Butter	Caster Oil	Coconut Oil	Cottonseed Oil	Lard	Linseed Oil	Menhaden Oil	Soybean Oil	Tung Oil
Butyric	Butanoic		4								
Caproic	Hexanoic		2		0.5						
Caprylic	Octanoic		1		8						
Capric	Decanoic		2		7						
Lauric	Dodecanoic	0.1	2		48		tr.		0.1		
Myristic	Tetradecanoic	3	12		17	0.5	1		7	0.1	
Palmitic	Hexadecanoic	29	25	2	9	21	28	6	16	8	4
Stearic	Octadecanoic	20	9	1	2	2	13	4	2	4	1
Arachidic	Eicosanoic	0.8				0.2		0.3		0.6	
Lignoceric	Tetracosanoic					0.3		0.2			
Myristoleic	9-Tetradecenoic	0.5	6 ^a				0.2		0.1	0.1	
Palmitoleic	9-Hexadecenoic	2	4		0.2		3		16	0.2	
Oleic	9-Octadecenoic	42	29	7	6	29	46	22	15	28	8
Linoleic	9,12-Octadecadienoic	2	4	3	2	45	6	17	7	54	4
Linolenic	9,12,15-Octadecatrienoic	0.5				2	0.7	51	3	5	3
Eleostearic	9,11,13-Octadecatrienoic										80
Arachidonic	9,12,15,18-Eicosatetrenoic	0.1					2		17		
Clupadonic	9,12,15,18,21-Docosapentenoic								11		
Ricinoleic	12-Hydroxy-9-octadecenoic			87							
Acids with over 22 carbon atoms									7		

^a Including lower unsaturated acids

lem. For example, a system having only two component fatty acid units has six possible triglycerides, AAA, AAB, ABA, ABB, BAB, and BBB (formulas of three of which are I-III). A system of three component acid units has eighteen possible triglycerides.

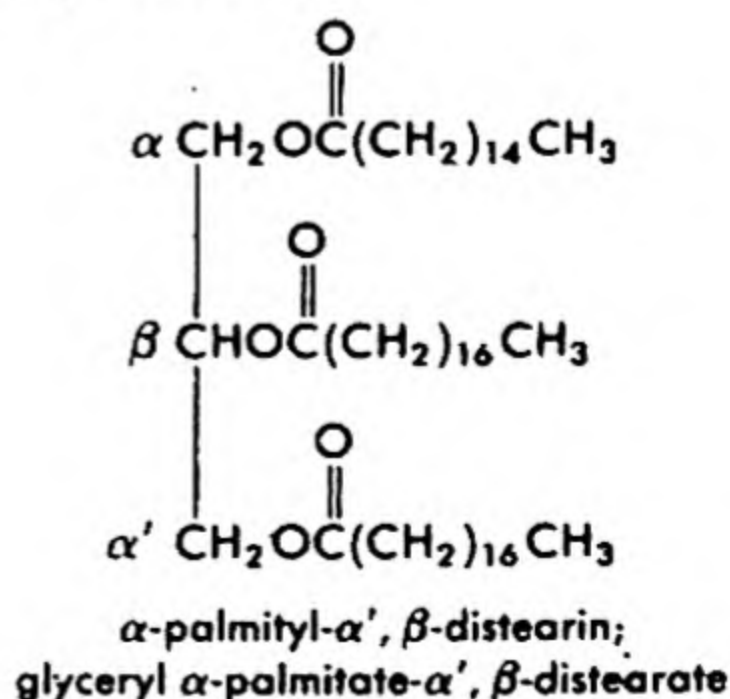
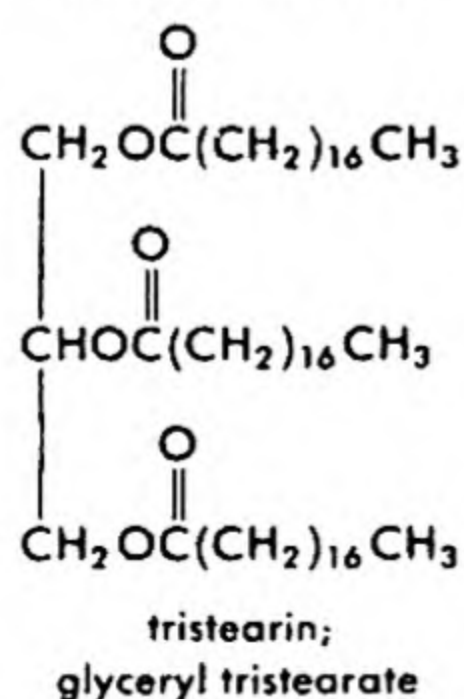


In order to get information concerning the distribution of acyl groups in fats, T. P. Hilditch oxidized the mixture of glycerides in various fats to cleave the multiple bonds. The free acid groups which remained at the chain ends formed salts, hence could be readily separated from the unoxidized saturated glycerides. Monoacidic, diacidic, and triacidic glycerides were then separated by fractional crystallization of their salts from suitable solvents. Simple analysis for dicarboxylic acids after hydrolysis of the glycerides gave the distributions of saturated and unsaturated acyl groups in the original fat. The work done thus far suggests that the distribution of acyl groups in a fat is essentially random.

The structures of the fatty acids obtained by hydrolysis of fats were ascertained by the usual methods of structural analysis. Geometric isomerism has been found in the fatty acids. Thus oleic acid is *cis*-9-octadecenoic acid, whereas elaidic acid, the isomer, is *trans*. When both isomers are available, they can be characterized by infrared spectra, which show fewer bands for the *trans* isomer and a C=C frequency about 20 cm^{-1} higher for the *trans* isomer.

D. Nomenclature

Several types of nomenclature systems are used to name glycerides. These are illustrated by the examples below. None of these are IUPAC rules names, which are so impracticable that they are never used. Greek letters are used where necessary to indicate positions.

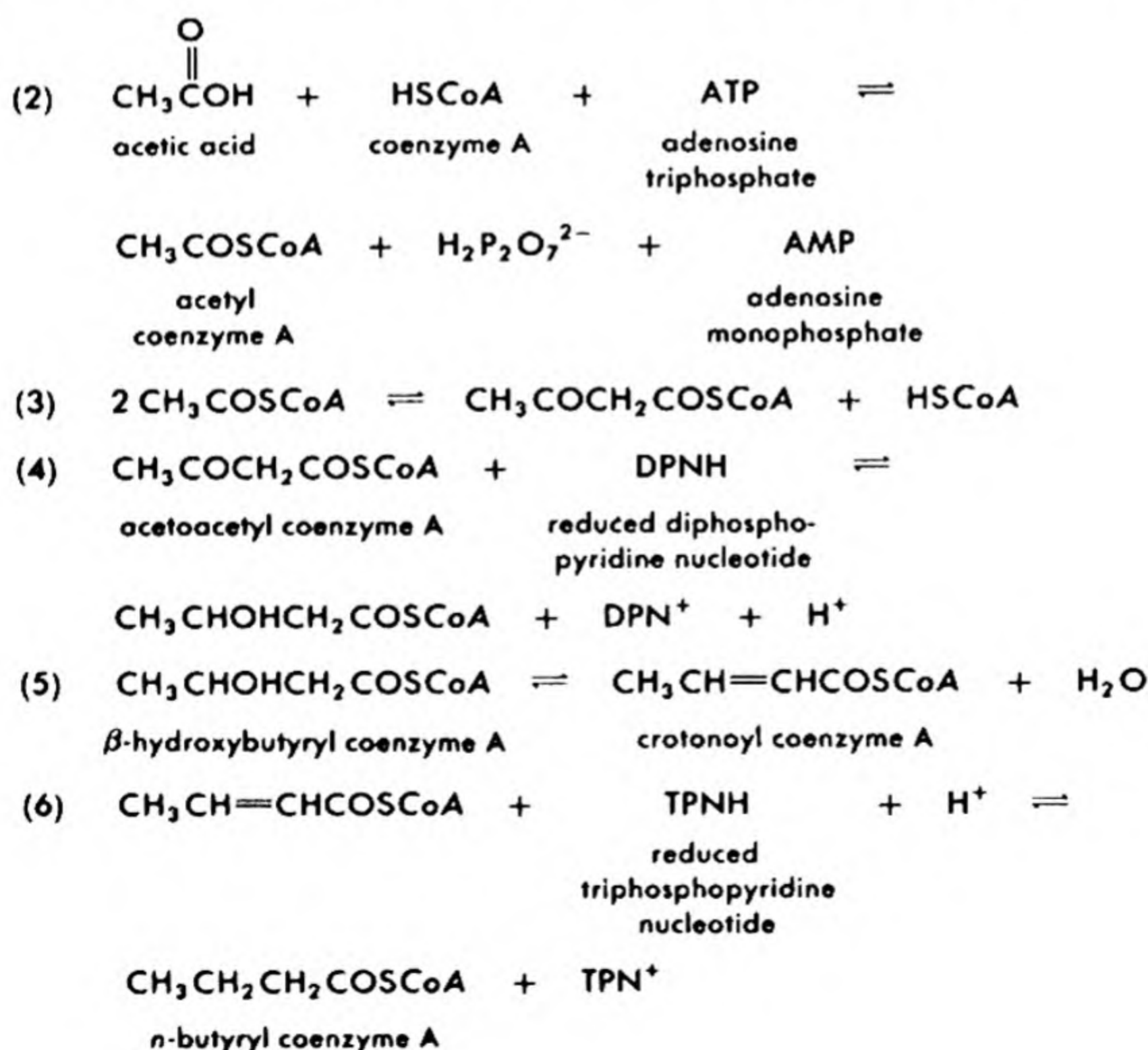


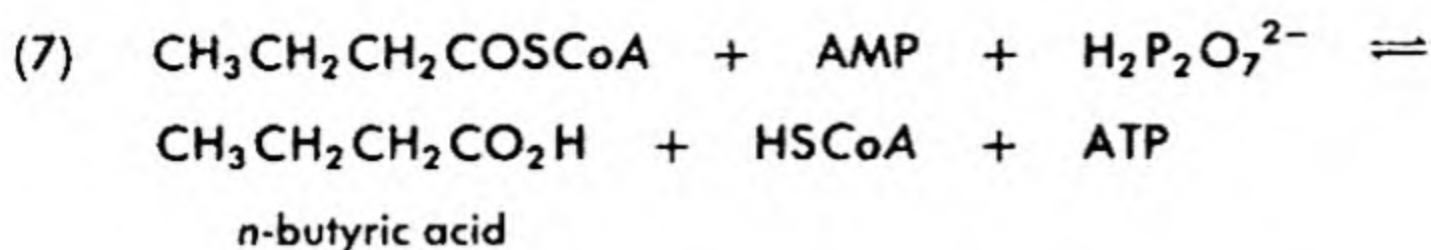
E. Biological Utilization of Fats and Oils

Simple lipids are of considerable metabolic importance, representing both dietary sources of energy and storage reservoirs of chemical energy. Oxidation of fats gives more than twice as many calories per unit weight as oxidation of carbohydrate material. For transport, dietary triglycerides are emulsified by bile salts (§41-2B). The triglycerides are partly hydrolyzed to fatty acids and monoglycerides or glycerol at the interface between the fat droplets and the aqueous solution of the enzyme lipase in the small intestine. The emulsified hydrolysis mixture is then transported through the intestinal wall and reconverted to triglycerides in the lymph system. Triglyceride is present in blood and is the state in which lipid is stored in body organs and tissues. Such stored fats are called *depot fats*.

F. Biogenesis and Oxidative Degradation of Fatty Acids

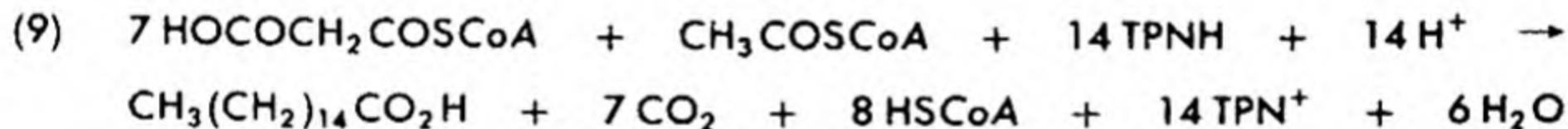
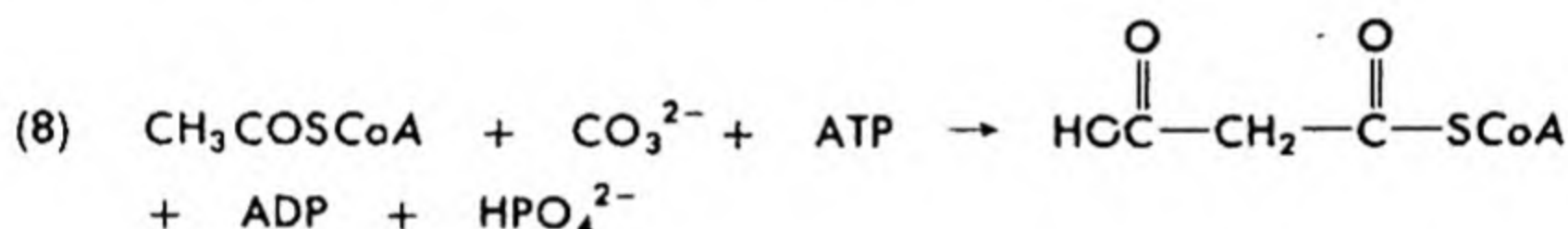
Organic chemists and biochemists have been interested in the chemistry of the biological synthesis of fatty acids and in their utilization by oxidation. While the details are left to more advanced texts, it is clear that both processes involve two-carbon fragments, derived from acetic acid. Thus, as an example, the interconversion of butyric acid and acetic acid occurs in mitochondria via the following sequence.





Each of the steps is catalyzed by an individual enzyme. The natures of the oxidation-reduction reagents, DPNH and TPNH, of the phosphorylated adenosines, ATP and AMP, and of coenzyme A are described in §39-3B.

Other mechanisms involving malonyl coenzyme A intermediates have been demonstrated, and it is clear that such mechanisms are generally more important than the mitochondrial synthesis. In these processes acetyl coenzyme A is converted enzymatically to malonyl coenzyme A (eq. 8), and this is then converted enzymatically to long-chain fatty acids in the presence of TPNH and acetyl coenzyme A. The stoichiometry of the formation of palmitic acid is given in eq. (9).



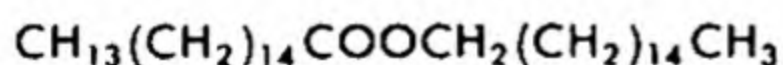
All mechanisms require that alternate carbon atoms in the fatty acid arise from the methyl carbon atom of acetic acid. Tracer experiments have demonstrated this.

40-2 WAXES

Waxes differ from fats in that they are esters of high molecular weight alcohols. Increasing industrial use of waxes has provided impetus to prepare wax-like synthetic materials by polymerization and to obtain special waxy fractions from petroleum. These synthetic and petroleum waxes are not lipids. (However, some hydrocarbons do occasionally occur in lipids, for example, squalene, §41-2.)

The fatty acids of which waxes are composed are of higher average molecular weight than those from fats. These acids in waxes are generally in the range of C_{16} to C_{36} . The alcohols are normal alcohols in the range of C_{16} to C_{36} or are sterols (§41-2B).

Spermaceti from the sperm whale is largely cetyl palmitate (hexadecyl hexadecanoate). Beeswax is rich in myricyl palmitate.



cetyl palmitate



myricyl palmitate

40-3 SOAPS AND OTHER DETERGENTS

The salts of fatty acids are commonly called soaps; alkali metal salts are in common use as detergents. These are somewhat costly, as the fats or oils from which they are derived have value as foods. They are also unsuitable for use in hard water, as the calcium and magnesium salts are insoluble in water. Also they cannot be used in acidic solution. Thus, they have been supplanted in large measure by synthetic detergents.

In general, only the alkali metal and ammonium salts of carboxylic acids are appreciably soluble in water. Salts of divalent or trivalent metal ions are insoluble, as are also those of monovalent heavy metals such as silver. In contrast to this behavior, nearly all the salts of sulfonic acids and alkyl acid sulfates are soluble in water.

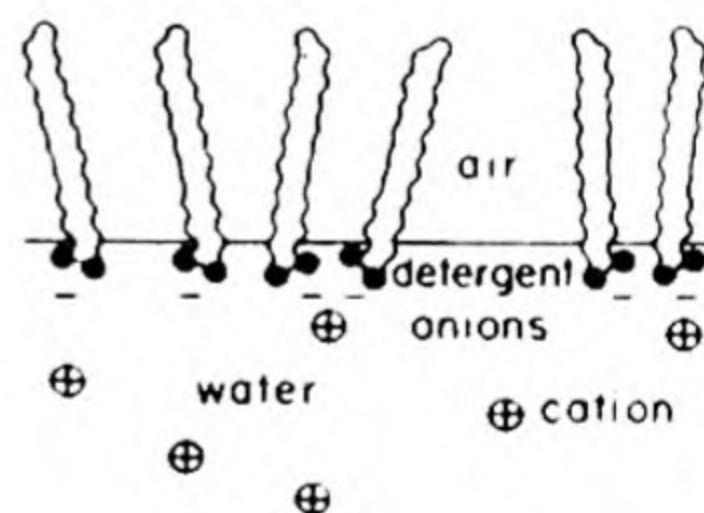
A. Colloid Chemistry of Detergents

Detergents, or cleaning agents, belong to one of several classes of *surface active agents (surfactants)*. These are materials which tend to concentrate at the surface, or interface, existing between two liquids or any two of the three states of matter. The surfactant has a strongly polar group to adhere or sorb to the polar medium and a large nonpolar group to orient toward the nonpolar medium.

Any surface or interface has a *surface tension*, or surface energy, caused by the unequal attractions between molecules on opposite sides. What the surfactant does is to tie together the two surfaces, thus diminish the fraction of dissimilar cohesions at the surface, and hence decrease the surface energy.

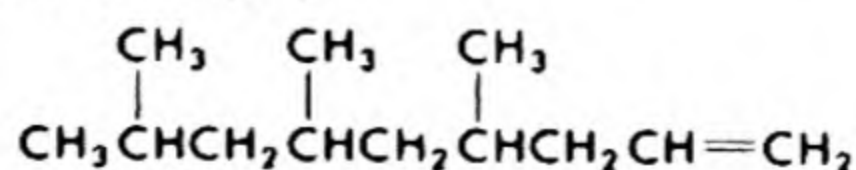
The way this operates is illustrated in several accompanying diagrams (Figs. 40-1-40-6).

Fig. 40-1. Orientation of Detergent Molecules at Surface of Water.



B. Manufacture of Detergents

The most widely used household and industrial detergent is a sodium alkylbenzenesulfonate. The raw materials are benzene, propylene, and sulfur trioxide or fuming sulfuric acid. The propylene is polymerized to give mainly a tetramer, largely



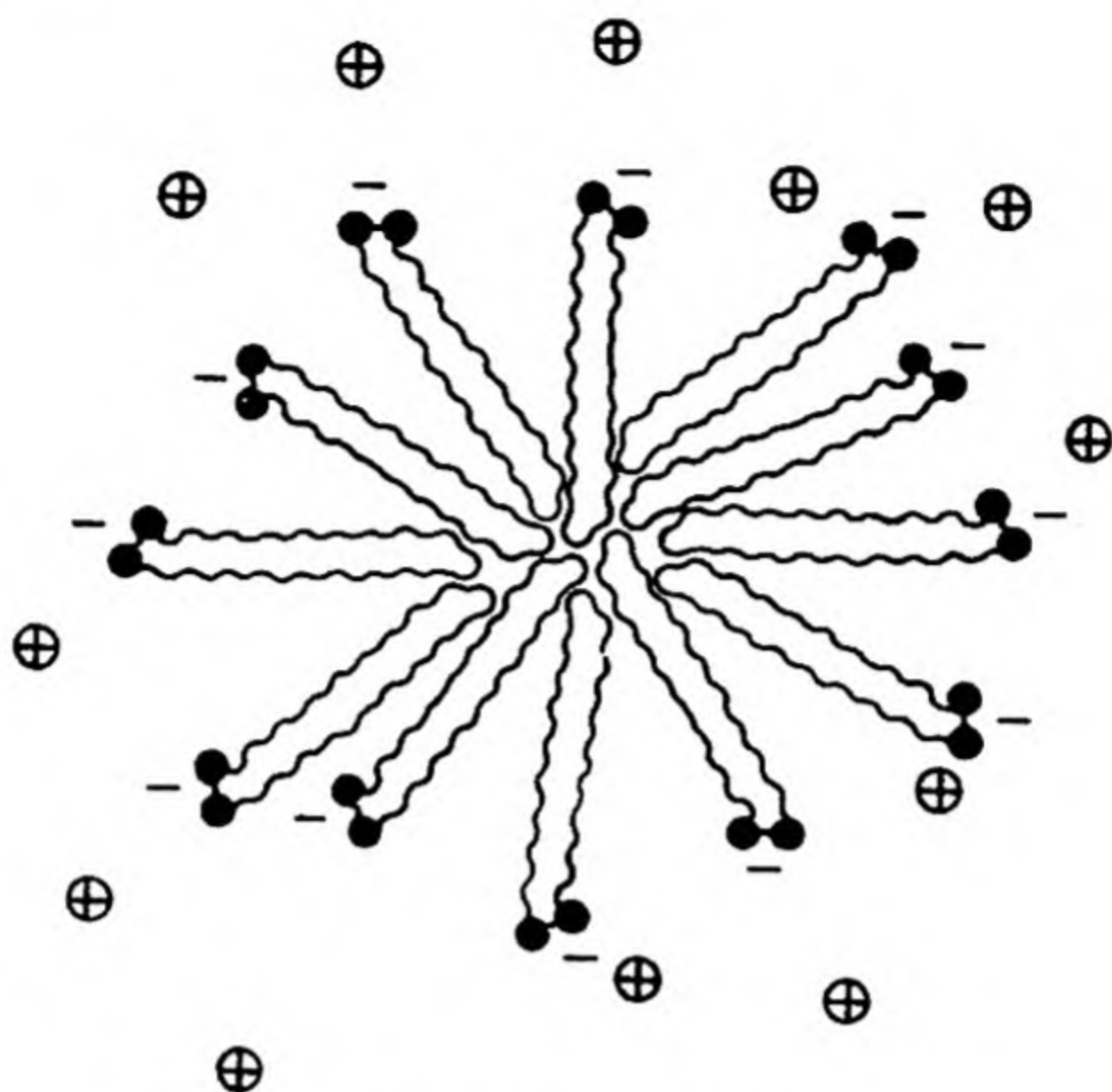


Fig. 40-2. Detergent Micelle.

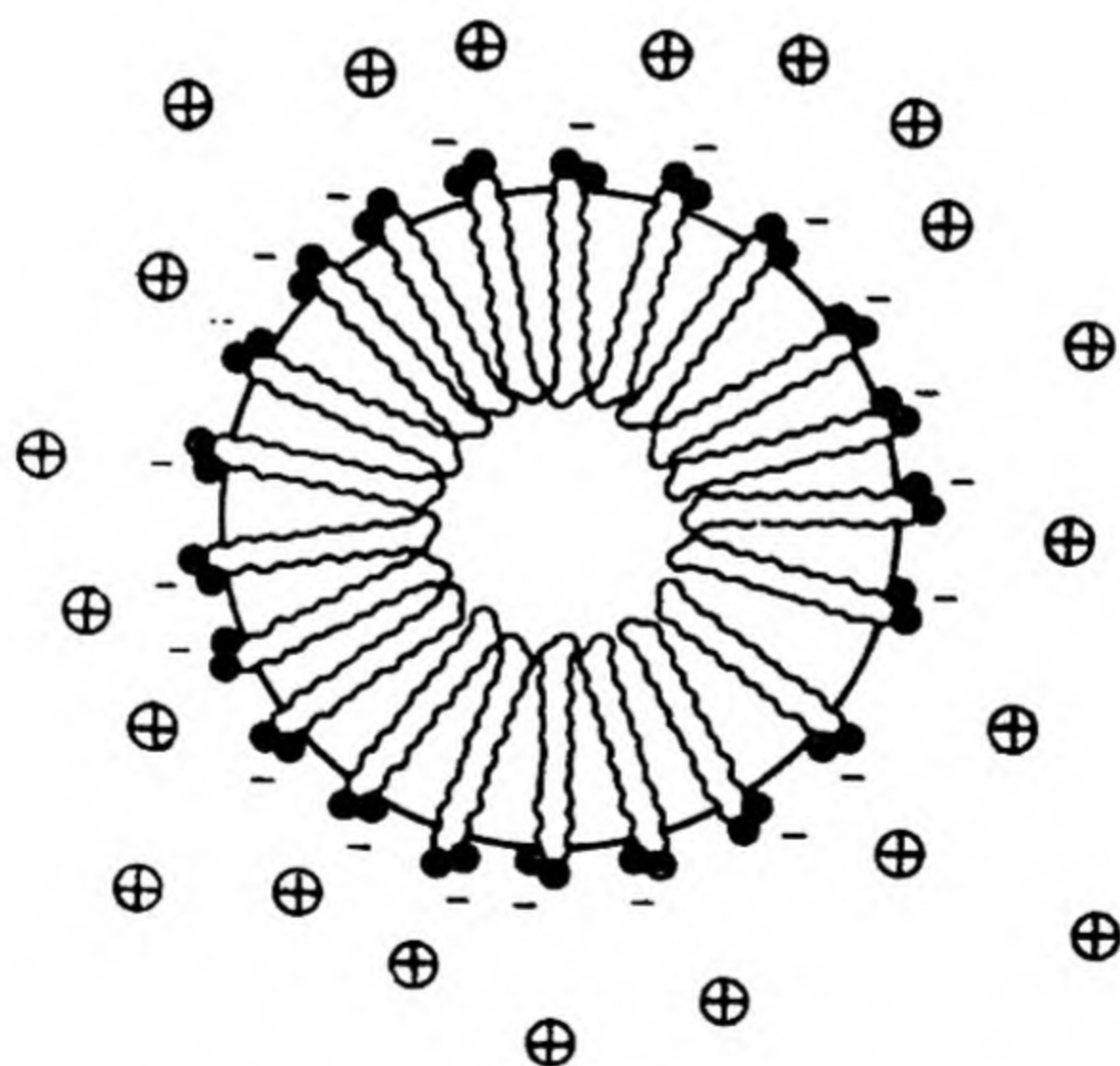


Fig. 40-3. Orientation of Detergent Anions in Oil Drop.

and isomers. This olefin is used to alkylate the benzene with sulfuric acid or hydrofluoric acid catalyst. The dodecylbenzene is then sulfonated. When sulfur trioxide is used, nearly all of the reagent is utilized. The sulfonic acid, with some sulfuric acid, is then neutralized with sodium

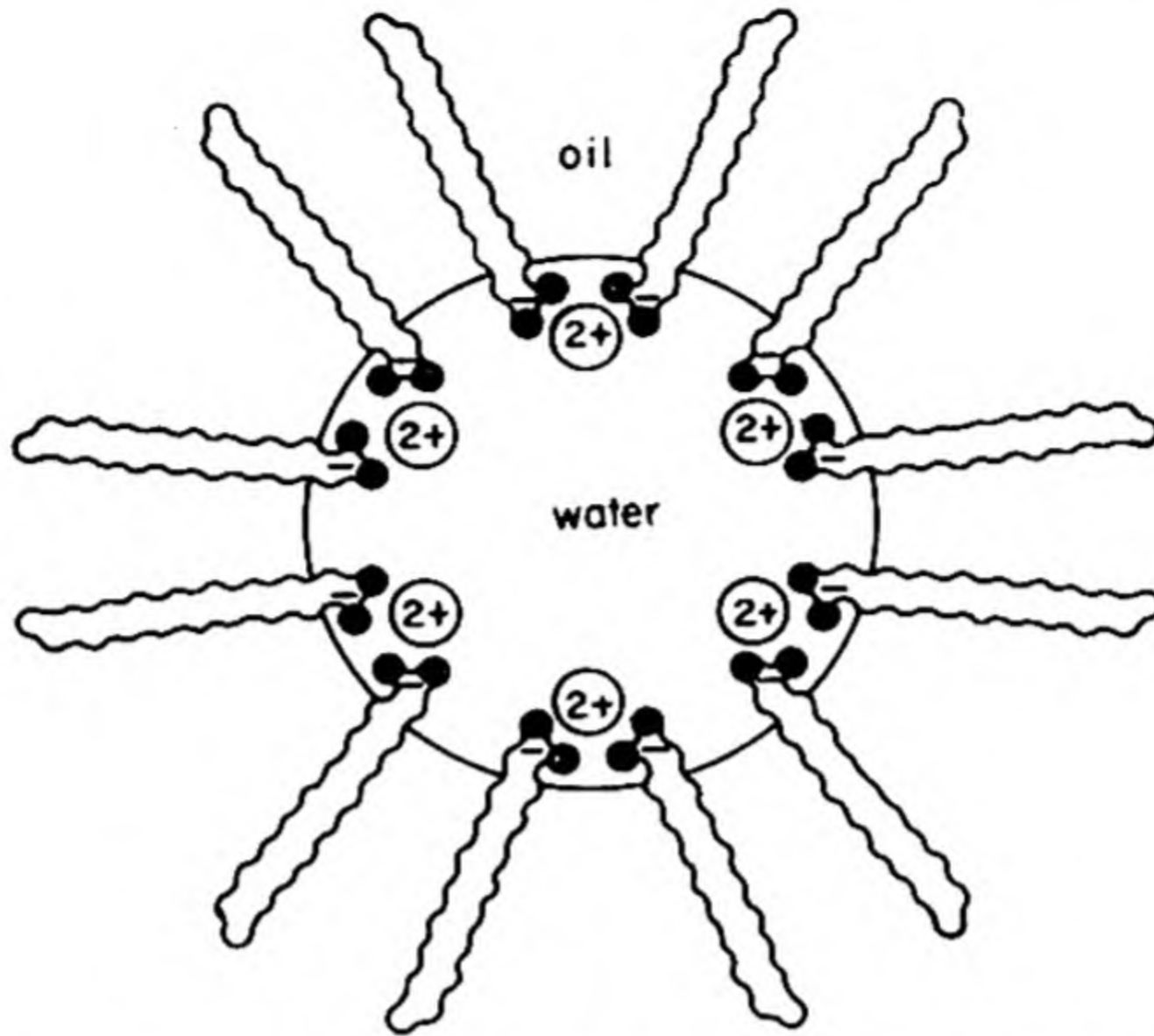
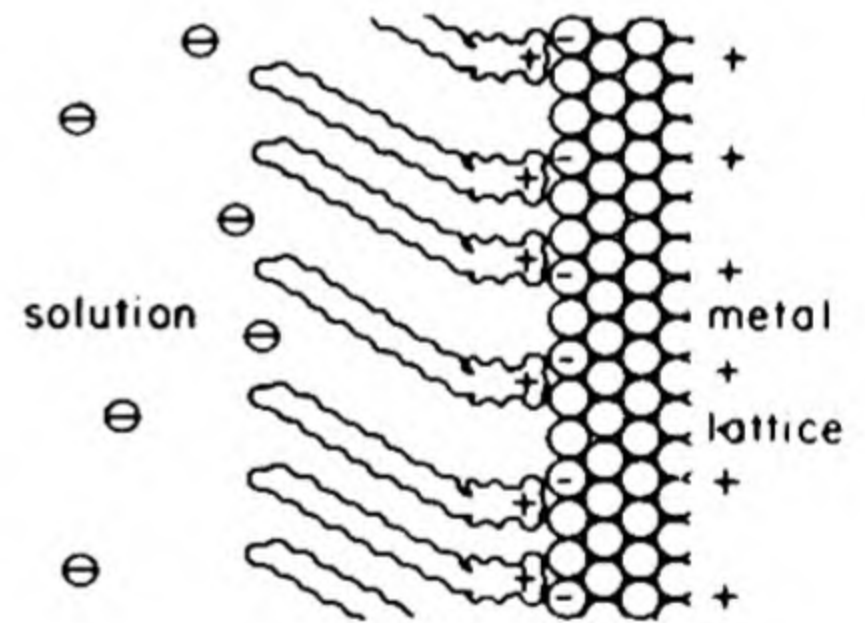


Fig. 40-4. Alkaline Earth Soap Forming Water-in-Oil Emulsion.

Fig. 40-5. Attraction of Cationic Surfactant to Metal Surface.



carbonate, to give a mixture of sodium dodecylbenzenesulfonates and sodium sulfate. The latter is important as a "builder," a material to improve soil-suspending and detergent action in the product. Other builders used are sodium tripolyphosphate and sodium carboxymethylcellulose. While these materials have little or no detergent action in themselves, they greatly enhance the detergency of the surfactants by favoring micelle formation at lower concentrations and increasing solubilization by coating the surface to be cleaned. (See Fig. 40-2.)

Sodium dodecylbenzenesulfonate was the most commonly used of all synthetic detergents until 1963. However, because of the methyl branches present on the alkyl side chain, microorganisms are unable to degrade it

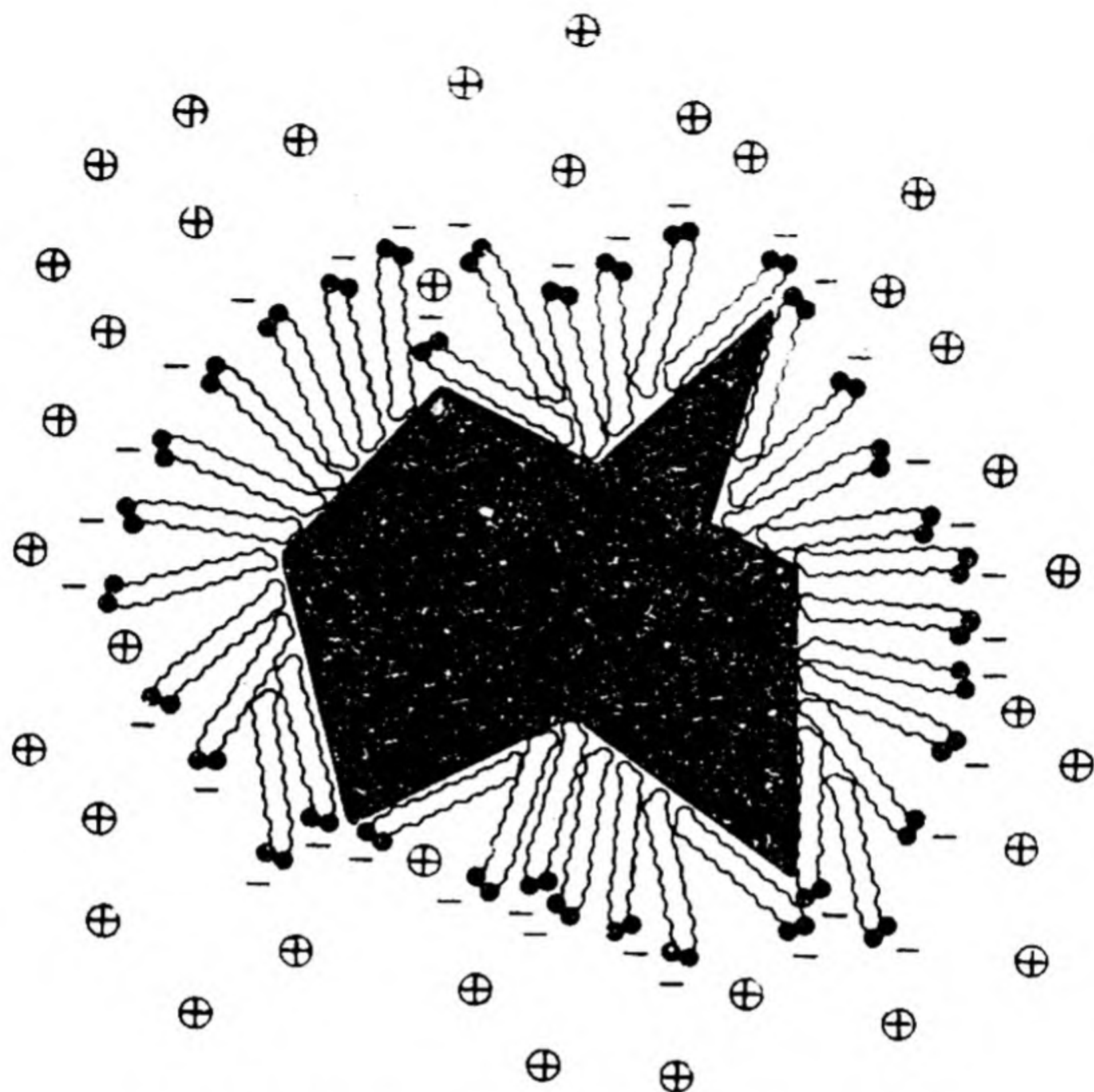
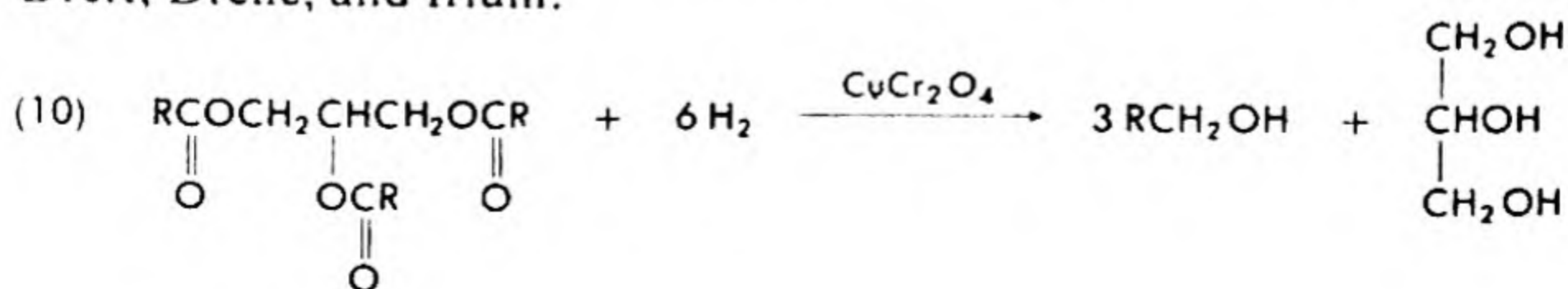


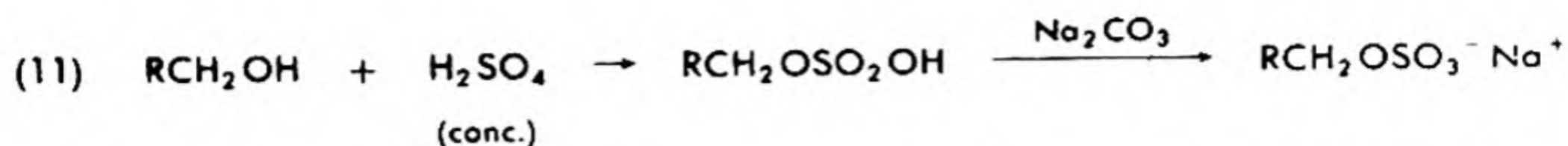
Fig. 40-6. Detergent Micelle with Absorbed Soil.

rapidly, and the disposal problem became so great as to make its use illegal in some countries. It is rapidly being displaced by the sulfonate prepared from the alkylation product of benzene with linear alkenes or linear alcohols. The products are *biodegradable* (i.e., degradable by microorganisms).

The next most widely used detergent type is a sodium alkyl sulfate. While the sulfonates are petroleum products, sulfates have been largely produced from fats. The fat is reduced by sodium and ethanol or by catalytic hydrogenation to glycerol and a mixture of fatty alcohols (eq. 10). The mixed or distilled alcohols are treated with sulfuric acid and neutralized (outline 11). Products containing sodium alkyl sulfates are Dreft, Drene, and Irium.

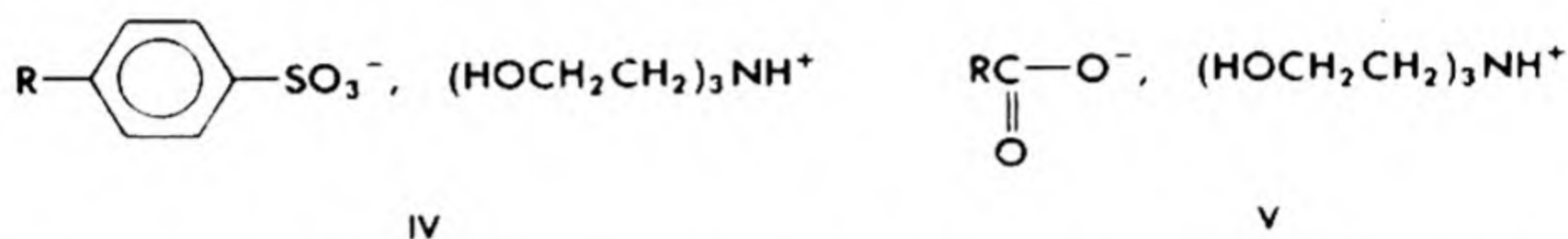


R is mainly $n\text{-C}_{11}\text{H}_{23}$ (from coconut oil).

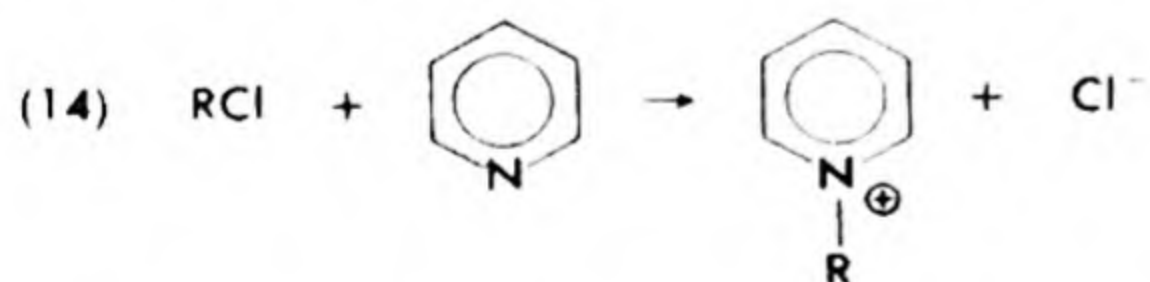
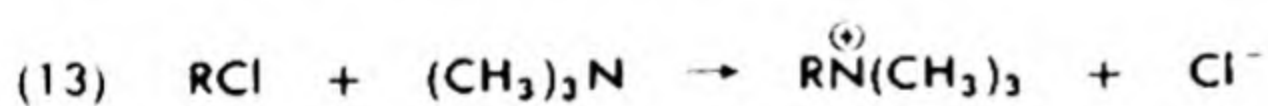
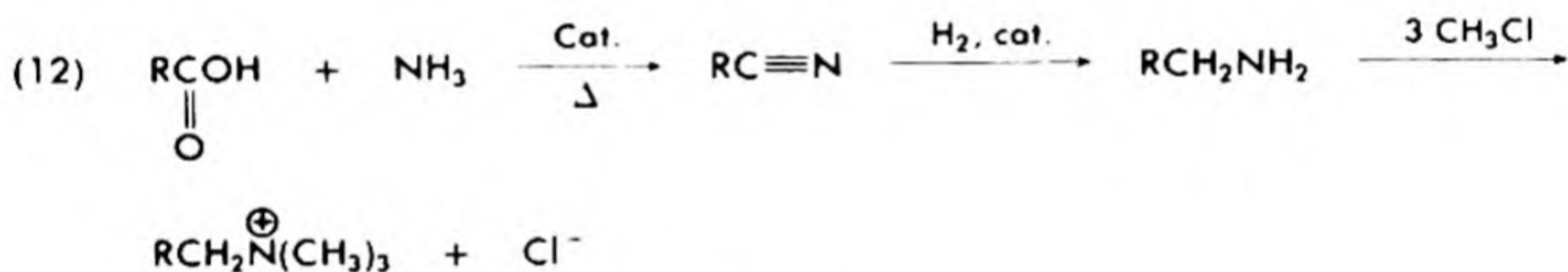


These materials, like the alkylarenesulfonates are salts of strong acids, so are effective in acid solution. Furthermore, the calcium and magnesium salts of both types are soluble in water, so that the detergents are useful in hard water. This is not true for salts of fatty acids.

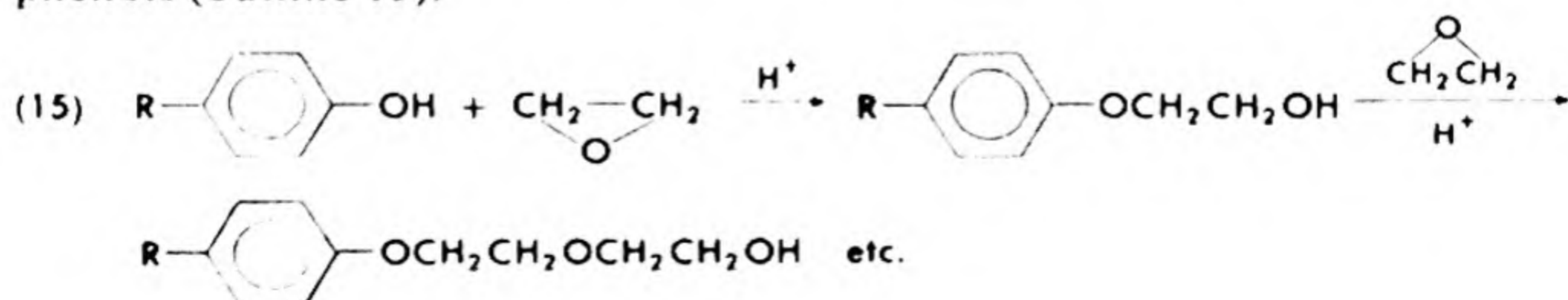
The very hydrophilic triethanolammonium ion can be used instead of the sodium ion so as to provide highly soluble materials for concentrated liquid detergents, IV. Triethanolammonium salts of fatty acids, V, are used in shampoos for similar reasons.



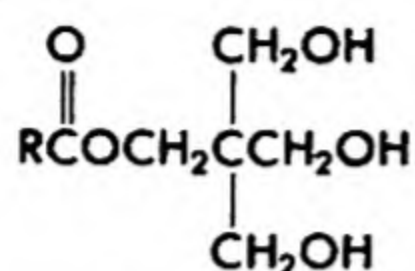
Cationic detergents or *invert soaps* are used mainly for germicidal properties. These detergents are prepared from fatty amines (outline 12) or from alkyl chlorides and tertiary amines (eqs. 13 and 14). An example is Cetab.



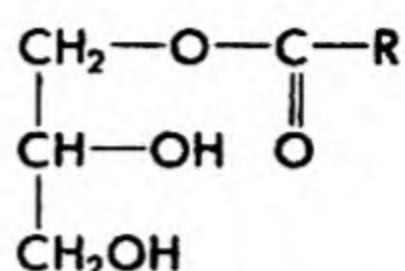
Nonionic detergents depend on polyfunctional hydrogen-bonding groups, rather than ionic charges, for their hydrophilic properties. One type contains polyether groups derived from ethylene oxide and alkylated phenols (outline 15).



Others are esters of polyhydroxy compounds, such as pentaerythritol monoalkanoates, and monoglycerides. The latter are edible, hence used as food emulsifiers.



a pentaerythritol monoalkanoate



a monoglyceride

Nonionic detergents have special advantages over ionic detergents for use in acidic and alkaline solutions. They can be tailor made to any desirable degree of polarity from surfactants that are mainly oil-soluble to those that are water-soluble, and they are compatible with either anionics or cationics, whereas the opposite ionic types precipitate each other.

Free fatty acids may be prepared directly from fats by acid-catalyzed hydrolysis. The catalyst is often *p*-toluenesulfonic acid (Twitchell reagent).

C. Other Products Related to Fats

Fats and fatty acids are important raw materials for industrial chemicals. The role of fatty alcohols, fatty acids, fatty nitriles, and fatty amines in the detergent industry has been indicated in the previous section.

Fatty alcohols, for example, can be converted to long-chain primary alkyl halides, esters of low volatility, such as 2,4-D esters (Table 43-4) for weed killers, and long-chain urethanes for fungicides.

Fatty amines are converted into salts of carboxylic acids, such as 2,4-D, 2,4,5-T, and acetic acid. The acetates are used as antistatic agents on plastic surfaces, corrosion inhibitors, bactericides, algacides, dispersing agents, and flotation agents.

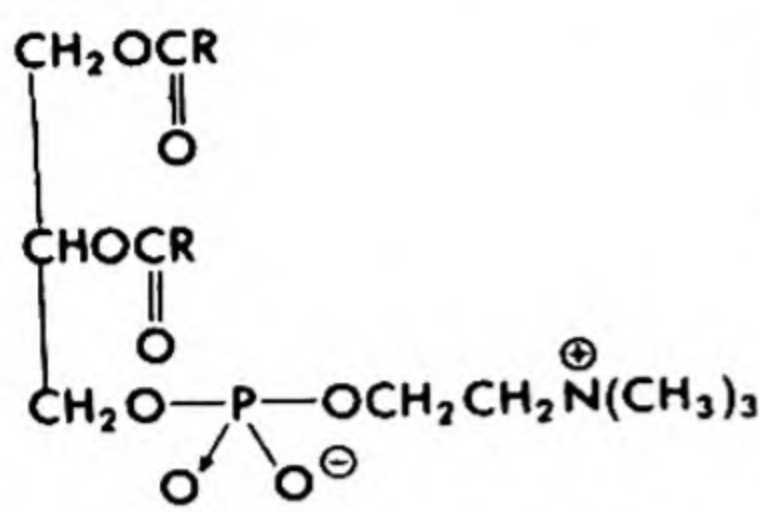
Fatty acids are converted to methyl esters for ease of refining before reduction or other conversions. Amides are produced from the fatty acids themselves or the esters. These amides are used to improve the workability and properties of rubber, to blend, supplement, and extend waxes, to improve adhesion of printing inks and varnish coatings to paper, to waterproof fabrics, and to promote foaming of detergents.

40-4 COMPOUND LIPIDS

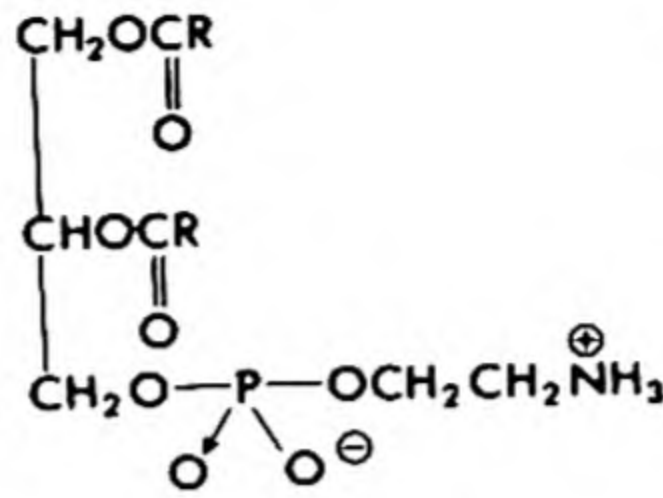
Compound lipids are the lecithins (also called phosphatidyl cholines), the cephalins (or phosphatidyl ethanolamines), the phosphatidyl serines, the acetal phospholipids (or plasmalogens), the phosphatidic acids, the phosphoinositides, and the phosphosphingosides. Nonphosphate compound lipids are also known.

The units of which the compound lipids are constructed are the fatty acids, glycerol, other polyols such as inositol, phosphate, and nitrogenous

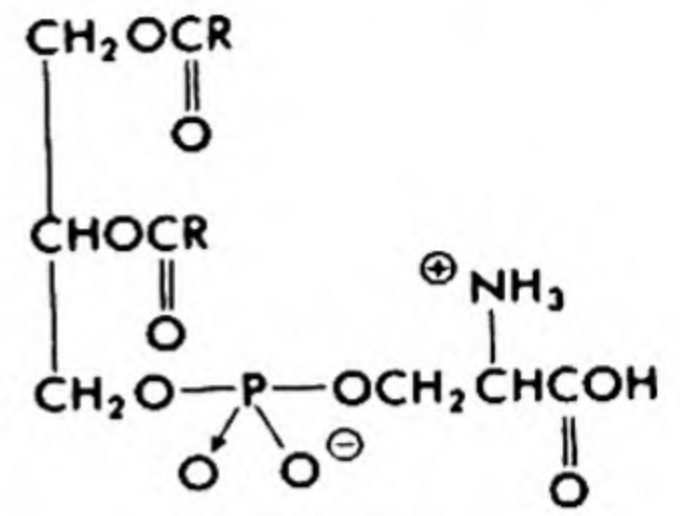
bases with hydroxy groups such as ethanolamine, choline, and sphingosine.



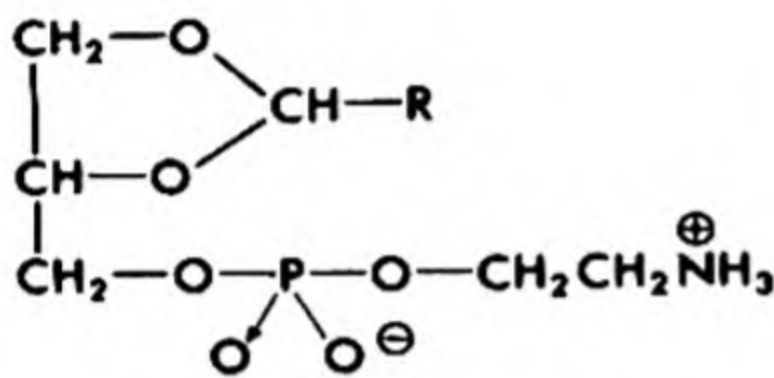
general formula for lecithins
(phosphatidyl choline)



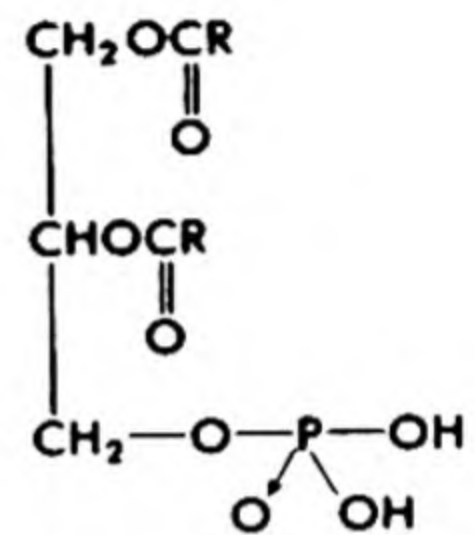
cephalins
(phosphatidyl
ethanolamines)



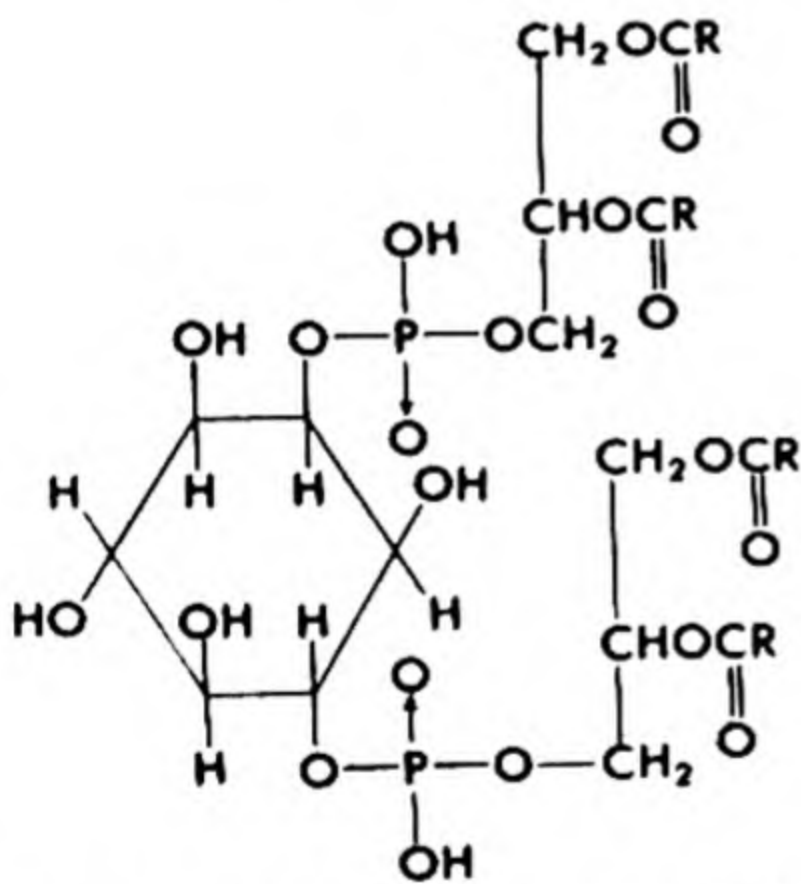
phosphatidyl serines



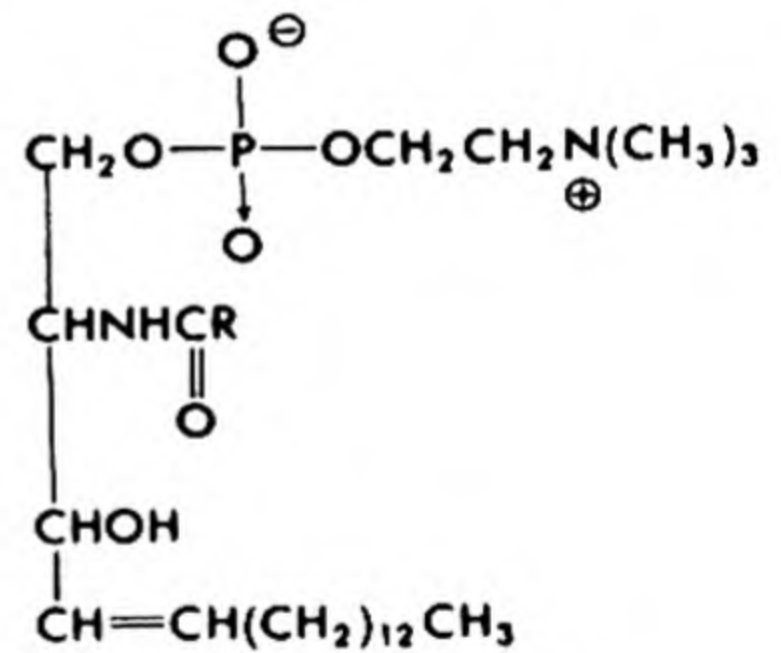
plasmalogens
(acetal phospholipids)



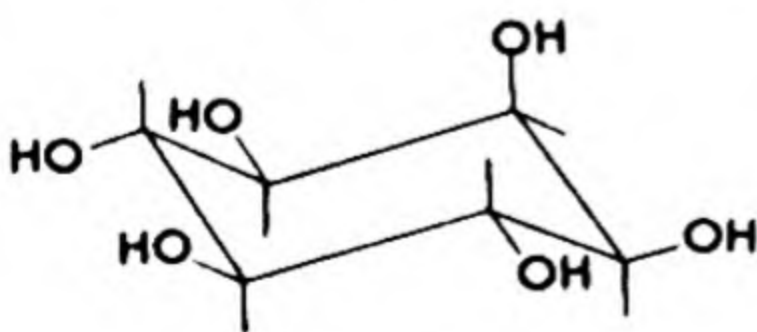
phosphatidic acids



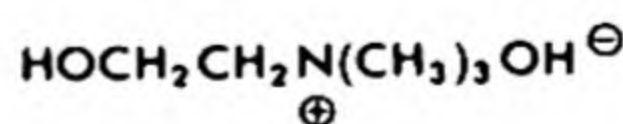
suggested formula for phosphoinositides
(still uncertain)



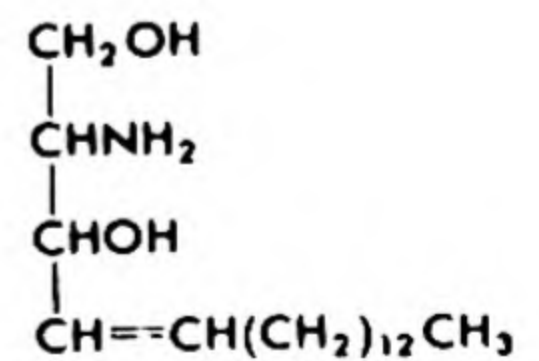
phosphosphingosides



inositol



choline



sphingosine

SUPPLEMENTARY READINGS

- Bloch, K. E., *Lipid Metabolism*, Wiley, New York, 1960.
 Cowan, J. C., and H. E. Carter, "Lipids," in H. Gilman, *Organic Chemistry, An Advanced Treatise*, Vol. III, Wiley, New York, 1953, pp. 178-242.
 Hanahan, D. J., *Lipid Chemistry*, Wiley, New York, 1960.
 Levey, M., "The Early History of Detergent Substances," *J. Chem. Educ.* **31**, 521-524 (1954).
 Snell, F. D., and C. T. Snell, "Syndets and Surfactants," *J. Chem. Educ.*, **35**, 271-278 (1958).
 White, A., P. Handler, and E. L. Smith, *Principles of Biochemistry*, 3rd Ed., McGraw-Hill, New York, 1964.

QUESTIONS AND PROBLEMS

- Write structural formulas of specific compounds (not formulas with "R") which represent the following terms.

a. saturated fat	e. nonionic surfactant
b. diglyceride	f. phosphosphingoside
c. lecithin	g. cephalin
d. wax	h. monounsaturated fat
- Write equations for the reactions that occur among the reagents listed together below. Use structural formulas for organic compounds. Specify essential special conditions.

a. tristearin + dilute hydrochloric acid	d. glyceryl trilinoleate + sodium + 2-decanol
b. α -oleyl- α' , β -dipalmitin + dilute sodium hydroxide	e. glyceryl trilinoleate + hydrogen + cupric chromite
c. glyceryl β -oleate- α , α' -dimyristoleate + iodine chloride	
- Write the structural formula for each compound named below. Calculate its iodine number.

a. trilaurin	c. dioleylglycerolphosphatidylcholine
b. glyceryl α -palmitate- β -oleate- α' -linolenate	
- Prove the existence of eighteen possible triglycerides containing one or more of three different fatty acids. Write structural formulas of the different compounds in the fat.
- Show how the following compounds could be distinguished by simple chemical tests. Describe the observed differences in behavior.

a. a saturated liquid fat and an unsaturated liquid fat	e. lecithin and a fat
b. butter and oleomargarine	f. stearic acid and tallow
c. beeswax and beef tallow	g. soap and sodium alkylbenzenesulfonate
d. beeswax and paraffin wax	

6. Explain how the molecular structure of a cationic surfactant makes it fit for effective use

- a. as a corrosion inhibitor on a metal
- b. as a water repellent on cement and ceramics

41

Terpenes and Steroids

41-1 TERPENES

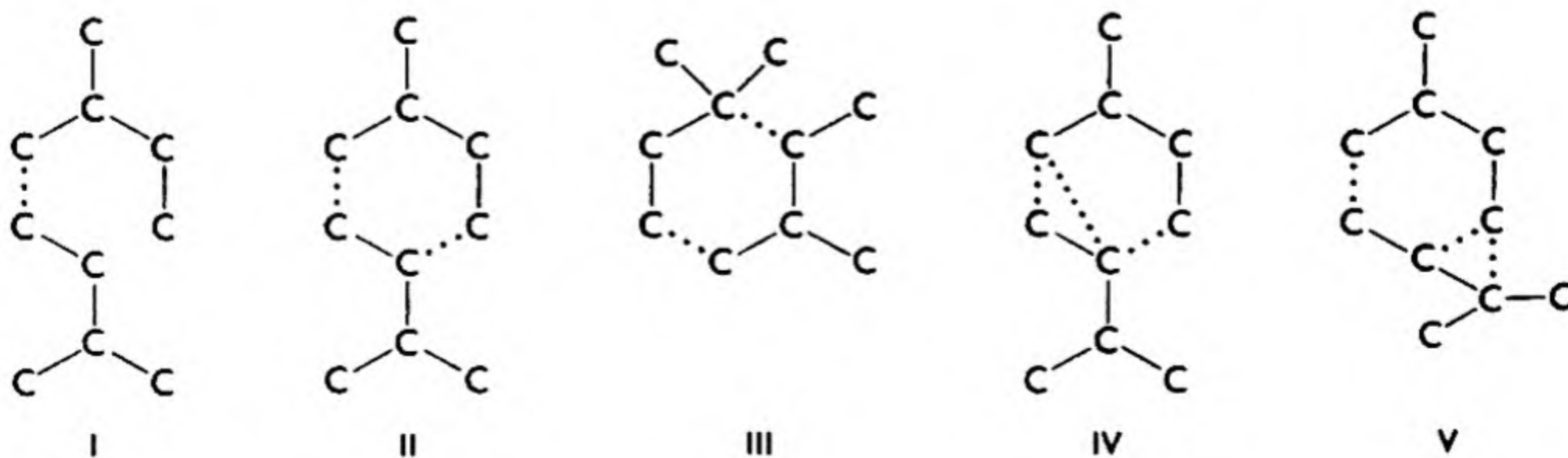
Terpenes are organic compounds produced by plants, characterized by carbon skeletons containing ten or multiples of ten carbon atoms. Monoterpenes have carbon skeletons with ten carbon atoms. Related compounds called sesquiterpenes, diterpenes, triterpenes, etc., have fifteen, twenty, or thirty carbon atoms and further multiples of the terpene framework.

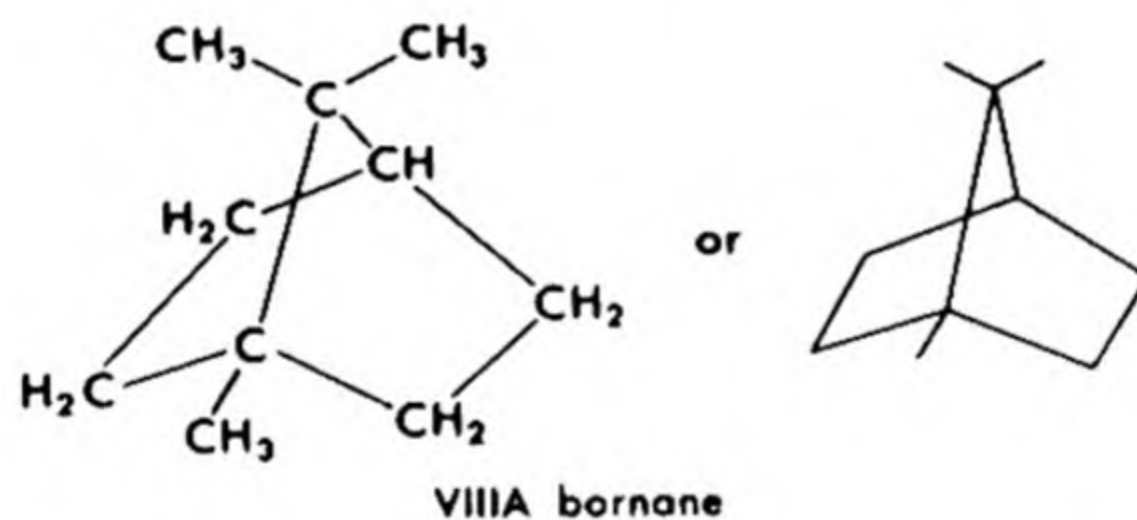
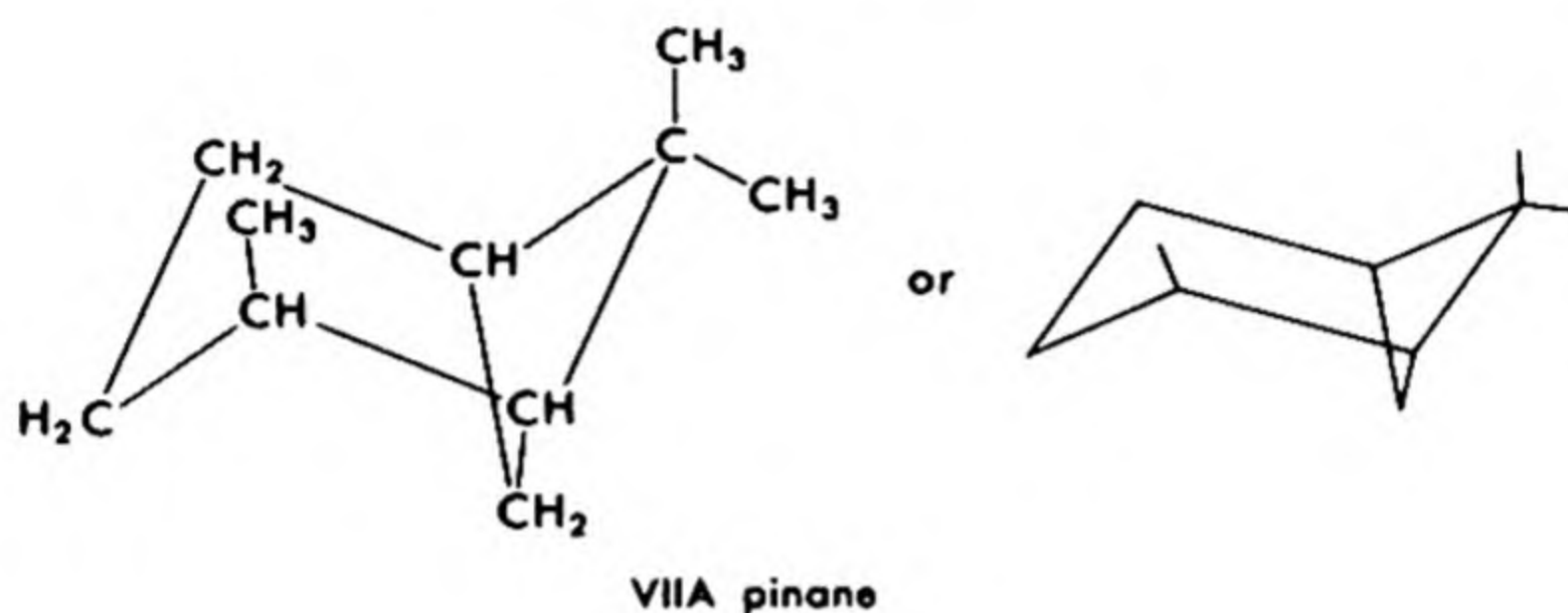
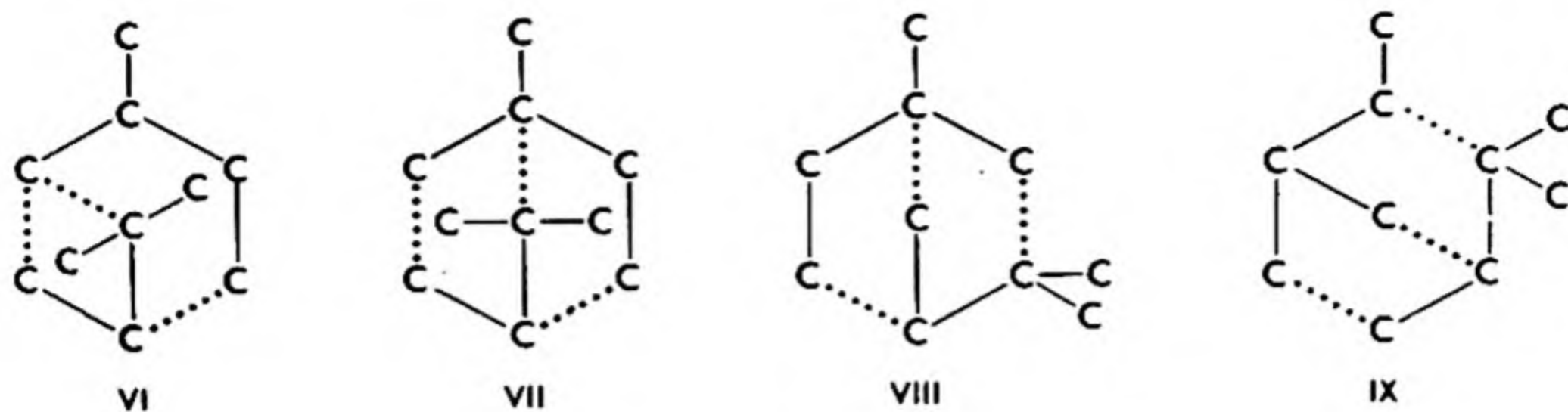
A. Isoprene and the Structure of Terpenes

All simple terpenes and most polyterpenes are built up in plants from units having the carbon skeleton of isoprene. The isoprene rule has been of great value in determining structures of terpenes. The isoprene units are indicated in some of the basic skeletal formulas given in following sections. This does not mean, however, that these compounds can be readily cleaved or synthesized at the indicated junctures or that all terpenes or polyterpenes follow the isoprene rule.

B. Monoterpenes

Monoterpenes are classified on the basis of their carbon skeletons as: acyclic, I; monocyclic, II and III; and bicyclic, IV-IX. In these formulas, dotted lines indicate bonds joining hypothetical isoprene units. (There is, of course, no fundamental difference between these bonds and any others in the same molecules.) Alternative formulations, VIIA and VIIIA, show



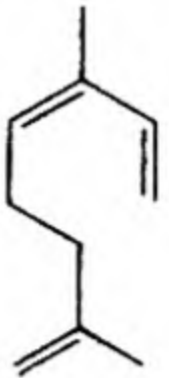
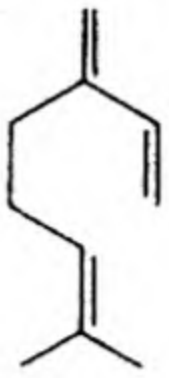
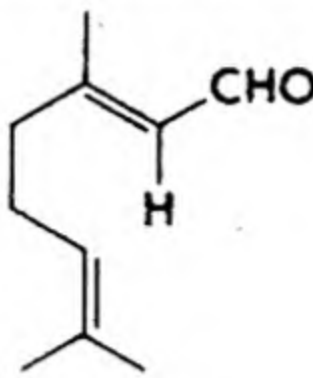
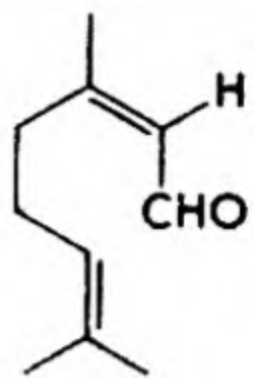
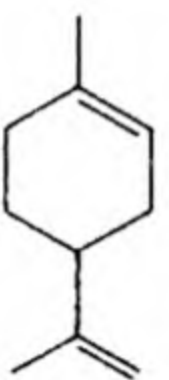
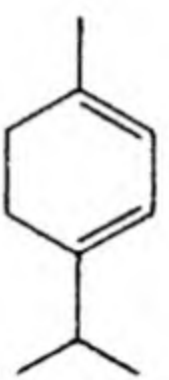
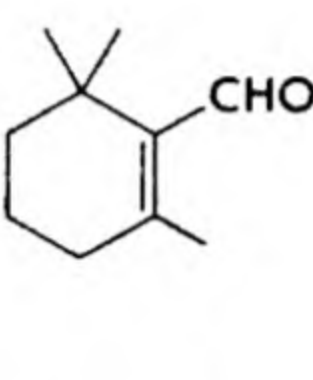
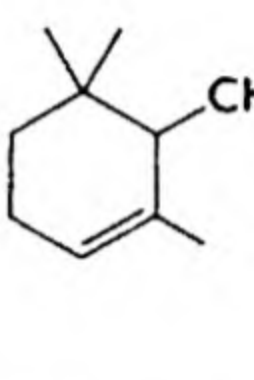
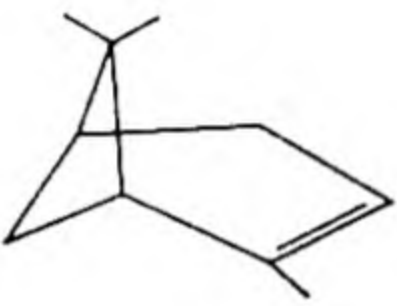
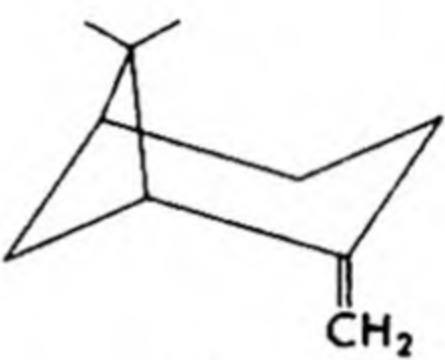
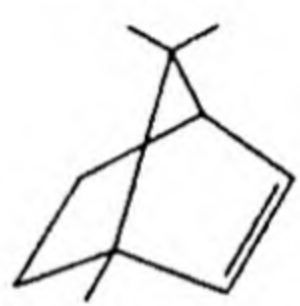
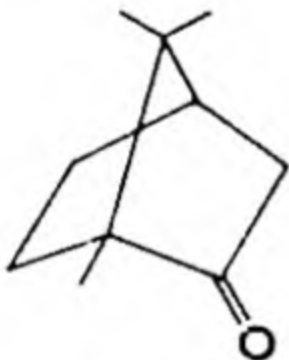
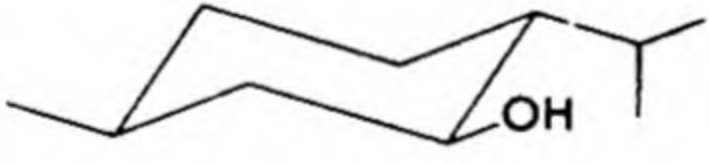
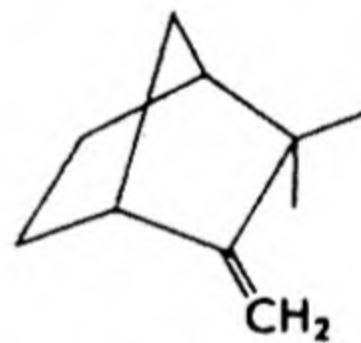


the spatial organization of the important bicyclic pinane and bornane systems. Side chain methyl groups are often represented by lines in terpene formulas. The structures of several representative monoterpenes are given in Table 41-1.

Terpenes may be classified narrowly to include only hydrocarbons, $(C_5H_8)_n$, or more broadly to include oxygenated derivatives of terpene hydrocarbons. We shall use the latter classification. Among the acyclic terpenes are the hydrocarbons ocimene and myrcene, the latter being the principal hydrocarbon constituent of oil of bay (the essential oil of bay leaves). Although ocimene is shown in Table 41-1 to have an isopropenyl

group, $CH_3-C=CH_2$, the hydrocarbon mixture actually contains material having an isopropylidene group, $(CH_3)_2C=$, as well. Ozonolysis of such mixtures, followed by reduction with zinc, gives acetone as well as formaldehyde. This is typical for many acyclic terpene derivatives.

TABLE 41-1. Some Monoterpenes and Derivatives

			
ocimene	myrcene	citral a geranial	citral b neral
			
limonene	α -terpinene	β -cyclocitral	α -cyclocitral
			
α -pinene	β -pinene	bornene	
			
camphor	menthol	camphene	

Acyclic aldehydes of importance are the citrals (geranial and neral), which are the major components of lemon grass oil. That these are α,β -unsaturated aldehydes is shown by high absorption at 2350 Å. Geraniol, the alcohol related to geranial, is found in geranium oil.

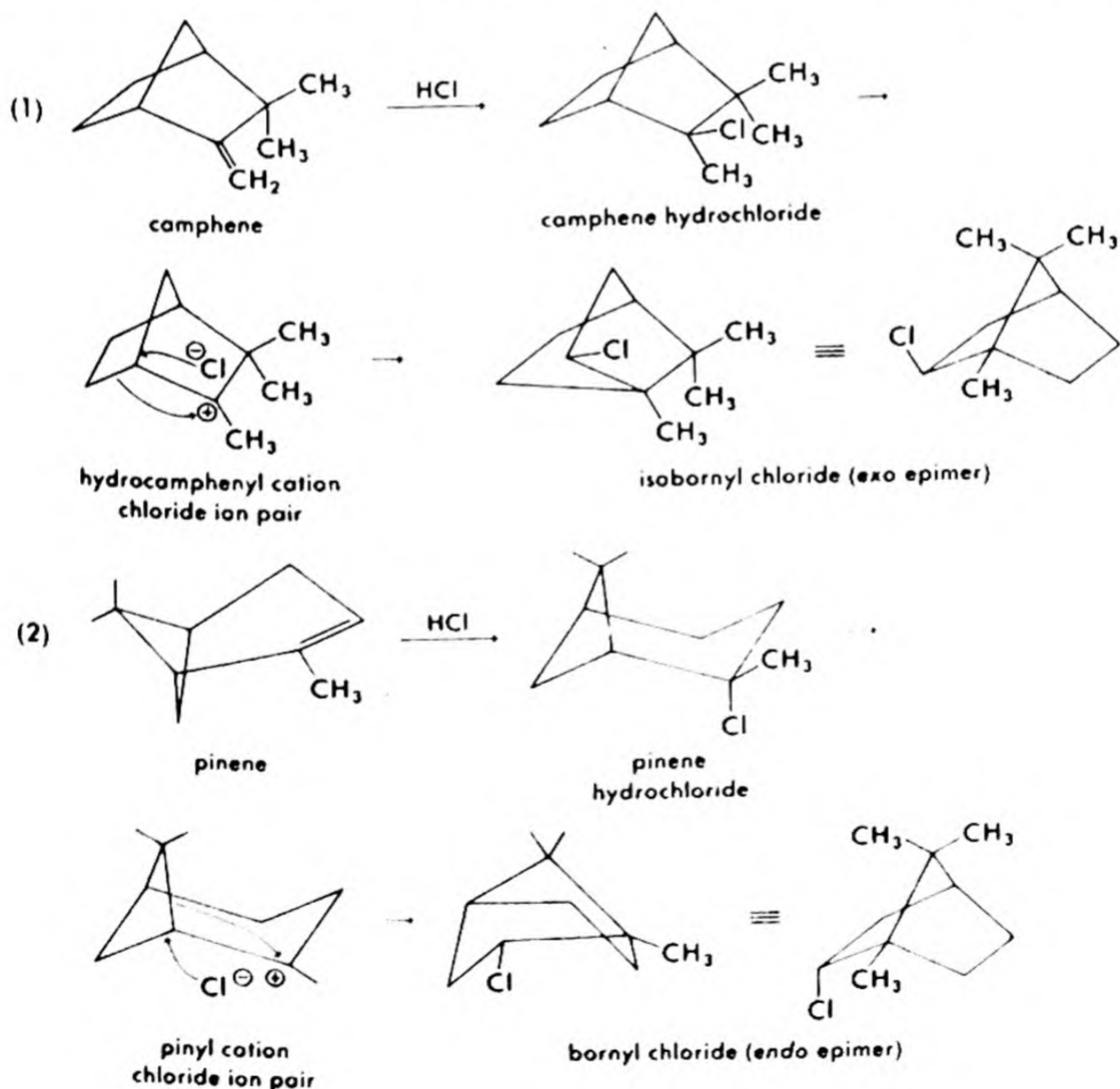
Monocyclic terpene derivatives may have the *p*-menthane ring skeleton, II, or the 2,2,6-trimethylcyclohexylmethyl structure, III. While natural monoterpenes are largely related to menthane, acid-catalyzed cyclization of citral gives a mixture of α - and β -cyclocitrals. Higher terpene derivatives have this ring system as well (see below).

Two important monocyclic terpene hydrocarbons are limonene (present in many essential oils and in turpentine) and α -terpinene (oil of marjoram). The alcohol, menthol, is a constituent of oil of peppermint and is widely used as a flavoring agent.

α -Pinene (a derivative of bicyclo[3.1.1]heptene) is the main constituent of turpentine, the oil secreted by conifers. The β isomer also occurs in turpentine. The bicyclo[2.2.1]heptene derivative, bornene, is not a natural product, although the related ketone camphor is produced in the camphor tree. The hydrocarbon camphene occurs naturally; it may also be prepared by acid-catalyzed rearrangement of pinene.

Among the many reactions of terpenes, the rearrangements are perhaps the most interesting. Studies in terpene chemistry added much to the knowledge of organic reaction mechanisms, in regard to both mechanisms of replacements and to mechanisms of skeletal rearrangements. At first these rearrangements caused much difficulty in the structural analysis of terpenes, but once recognized, they contributed helpful information.

Of the rearrangements two of the most thoroughly studied are the Wagner-Meerwein rearrangements of camphene hydrochloride (outline 1) and α -pinene hydrochloride (outline 2). Epimeric bornyl chlorides are produced, indicating stereospecific Walden inversions during the reaction.



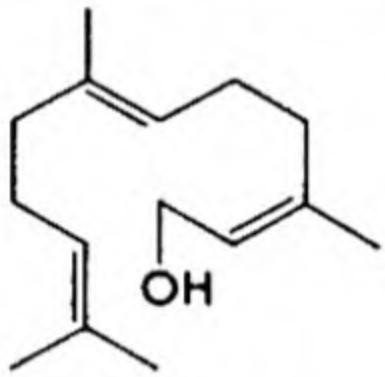
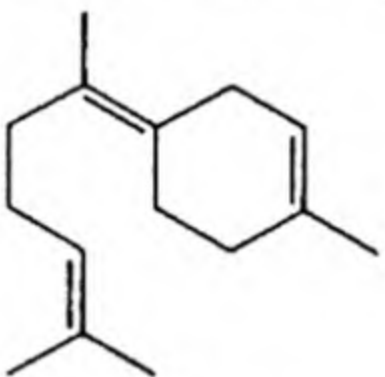
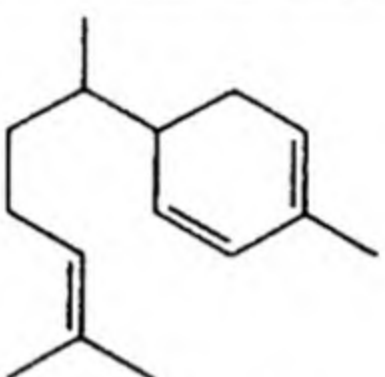
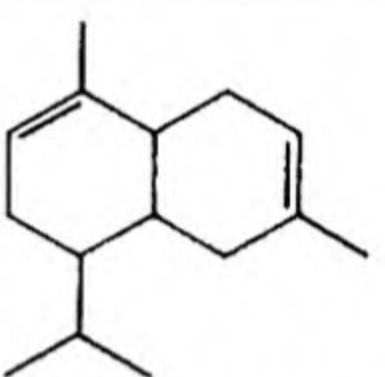
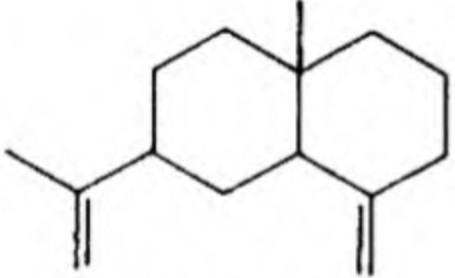
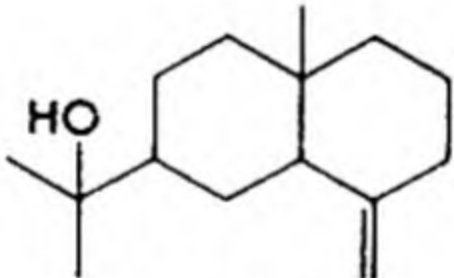
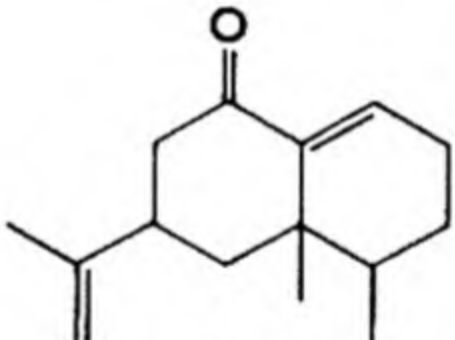
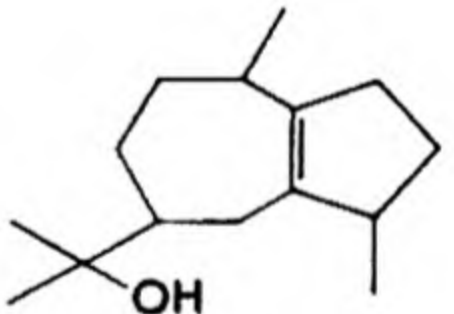
Reactions which typically rearrange terpenes are dehydration, addition of hydrogen halides, replacement of hydroxy groups with halogen atoms and vice versa, and treatment with strongly acid solutions. These all involve carbonium ion formation.

In respect to such reactions as oxidation, ozonization, nitrosation, condensations, diene synthesis, and reduction, all of which have been used for structural analysis of these compounds, terpenes usually behave normally.

C. Sesquiterpenes

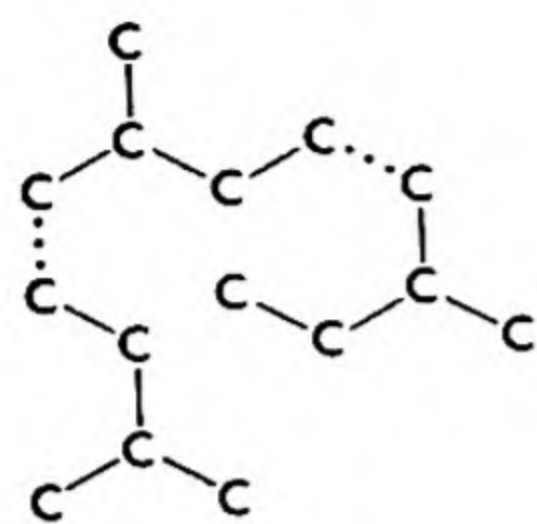
Several representative sesquiterpenes are given in Table 41-2. Skeletal types are acyclic, X; monocyclic, XI; bicyclic, XII, XIII, XV, and XVI; and tricyclic, XIV, XVII, and XVIII.

TABLE 41-2. Some Typical Sesquiterpenes

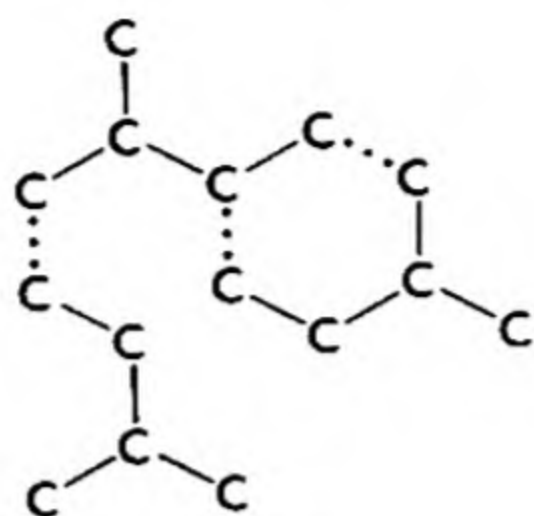
			
farnesol, in oils of various flowers	bisabolene, in oils of bergamot and myrrh	zingiberene, in oil of ginger	cadinene, widely distributed, especially in oil of cubeb
			
selinene, in celery oil	eudesmol, in eucalyptus oil	eremophilone, from an Australian shrub	guaialol, in guaiac wood oil

Dehydrogenation with sulfur and selenium have proved to be invaluable in the determination of structures of sesquiterpenes. Four products are obtainable, depending on the skeletal arrangements. Skeletal types X, XI, XII, and XIV form cadalene, XIX, upon dehydrogenation. Skeletal type XIII loses the angular methyl group and forms eudalene, XX. Skeletal type XV forms vetivazulene, XXI. Skeletal types XVI, XVII, and XVIII form guaiazulene, XXII, the last two by cleavage of the three-membered ring at the bridge bond common to the two six-membered rings.

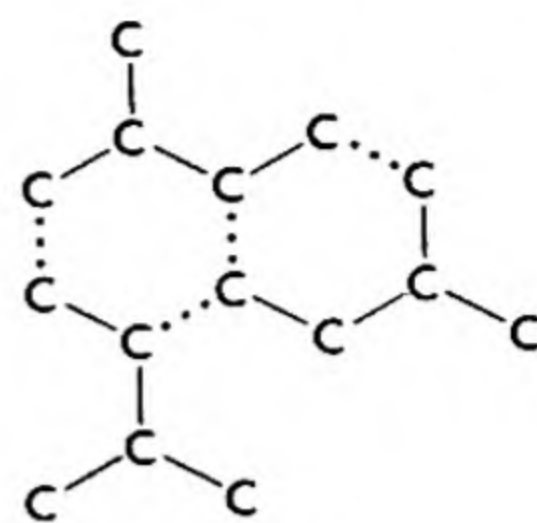
The skeletal type, XXIII, of which eremophilone was the first observed example, dehydrogenates to eudalene, but cannot be constructed of iso-



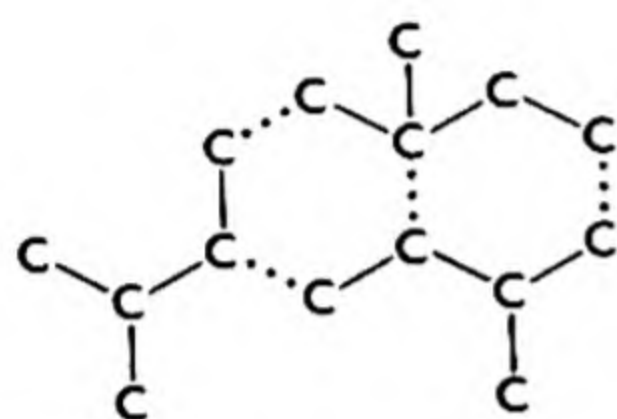
X



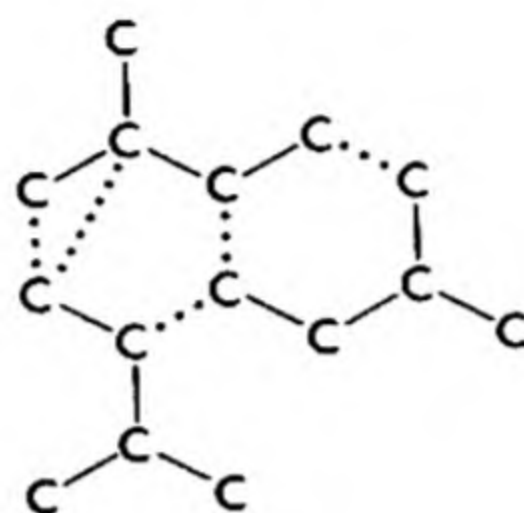
XI



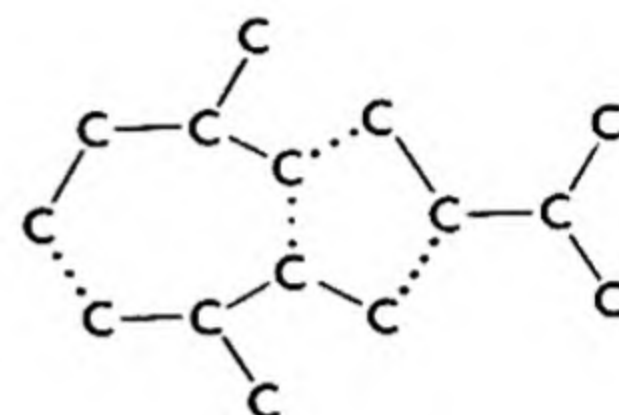
XII



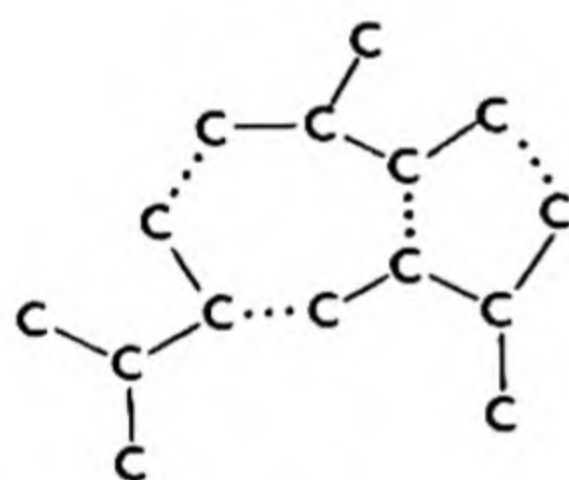
XIII



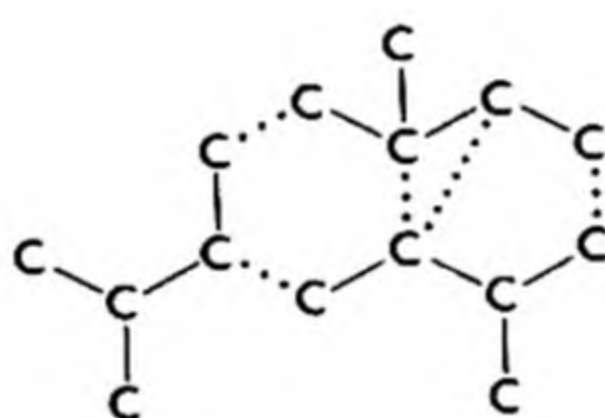
XIV



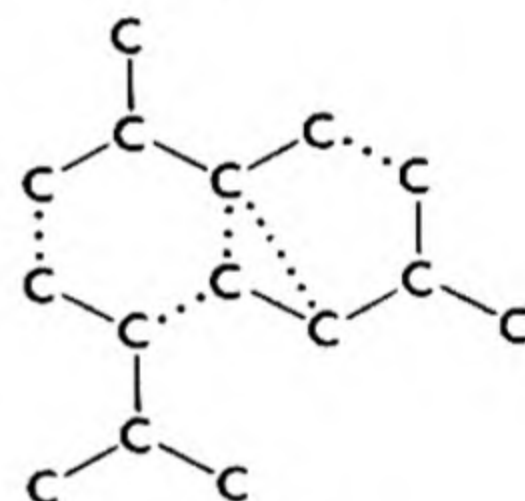
XV



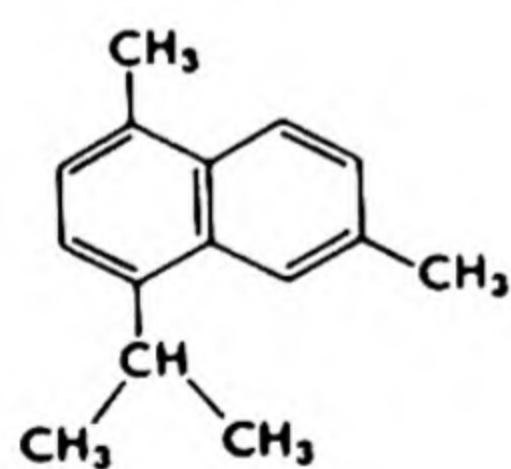
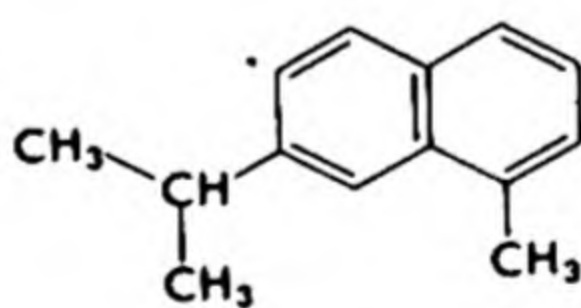
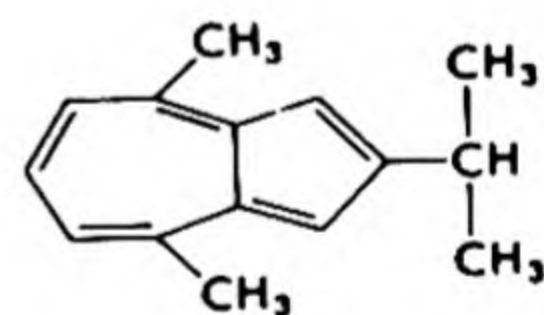
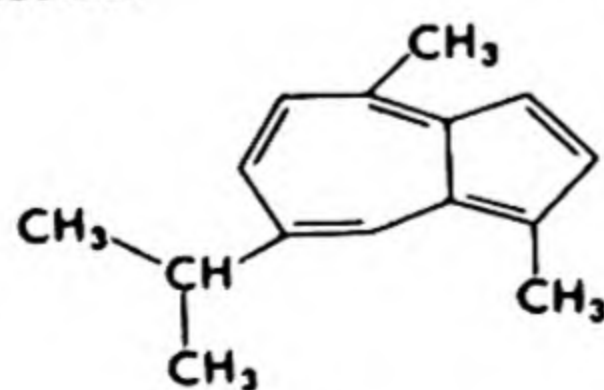
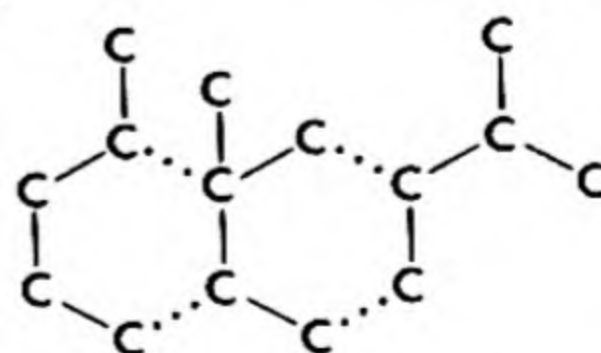
XVI



XVII



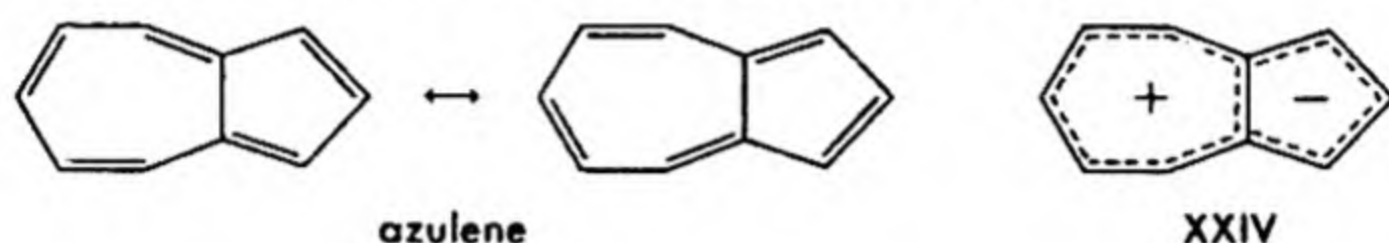
XVIII


XIX
cadalene

XX
eudalene

XXI
vetivazulene

XXII
guaiazulene


XXIII

prene units. Such nonisoprene structures are believed to be formed by Wagner-Meerwein rearrangements during biosynthesis.

The azulene derivatives were first noted by the development of blue colors during heating or oxidation of certain sesquiterpenes. Azulene itself is a deep blue (Sp., *azul*, blue), and it and its derivatives provide another example of a nonbenzenoid aromatic system (10 π electrons). The two major valence-bond structures for azulene are shown, as well as a hybrid formula, XXIV, showing a dipole moment.



D. Diterpenes, Triterpenes, and Tetraterpenes

A number of physiologically active compounds belong to the classes of di- to tetraterpenes. A number of industrially important resins and gums also belong to this class. Several are listed in Table 41-3.

TABLE 41-3. Occurrence of Di-, Tri-, and Tetraterpenes

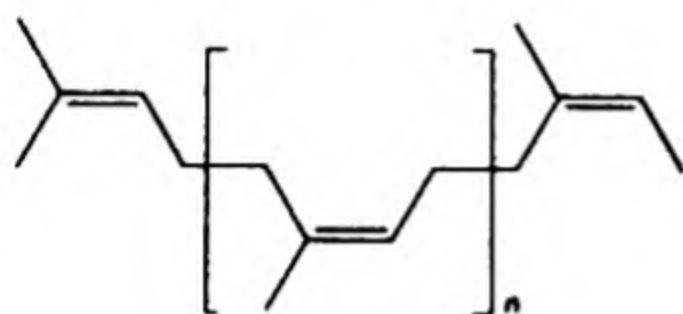
Name	Structure	Occurrence
<i>C₂₀</i>		
Vitamin A ₁		Fish liver oils; forms retinene ₁
Retinene ₁ Retinal (all <i>trans</i>)		Rhodopsin (visual purple). Important in the mechanism of vision
Agathic acid		Copal resins
Abietic acid		Pine resin, turpentine, tall oil. Rosin, a mixture of diterpene acids, is a sizing agent. Its salts are detergents, frothing agents, and clay sol stabilizers.
Pimaric acid		Pine oleoresin, tall oil

TABLE 41-3. Occurrence of Di-, Tri-, and Tetraterpenes (Cont.)

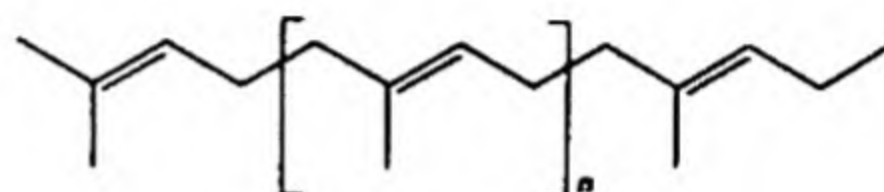
Name	Structure	Occurrence
C₃₀		
Squalene		Shark liver oil; an intermediate in biosynthesis of sterols
Oleanolic acid		As a glycoside derivative in guaiac bark and sugar beet; free in olive and mistletoe leaves
Lanosterol		Constituent of wool fat (lanolin)
C₄₀		
Lycopene		Red pigment of tomato and watermelon
Xanthophylls:		
Zeaxanthin		Corn, egg yolk
Rhodoxanthin		Red berries
Cryptoxanthin		Widely distributed; one of a number of provitamins A (compounds which are converted to vitamin A in the living organism)
Carotenes:		
α , R =		Widely distributed in plants, especially red and yellow roots and fruits. Provitamins A.
β , R =		

E. Polyterpenes

The two most important polyterpenes are India rubber and gutta-percha (balata). Both materials are mixtures, the main constituents of which are polyterpene hydrocarbons. The polyterpenes differ in that rubber is all *cis* in configuration, gutta-percha hydrocarbon all *trans*. Freshly precipitated rubber is soft, elastic, and sticky, whereas precipitated gutta-percha is hard and horny.



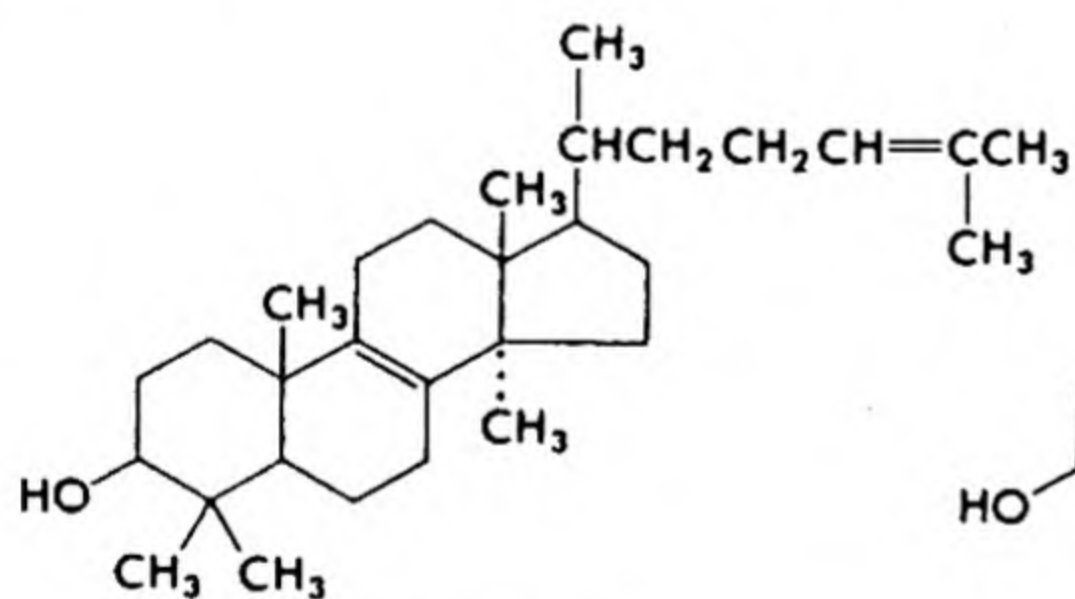
rubber



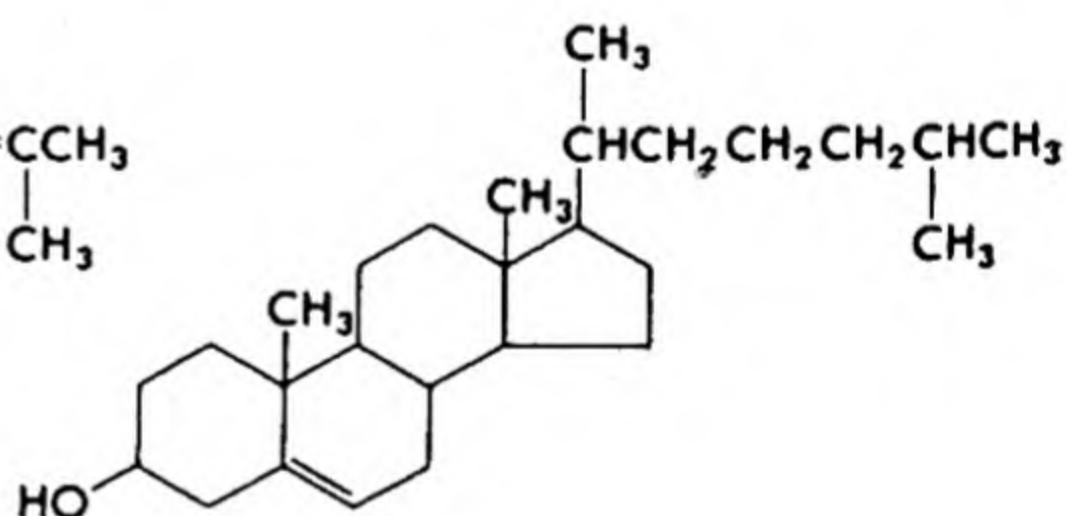
gutta-percha

41-2 STEROIDS

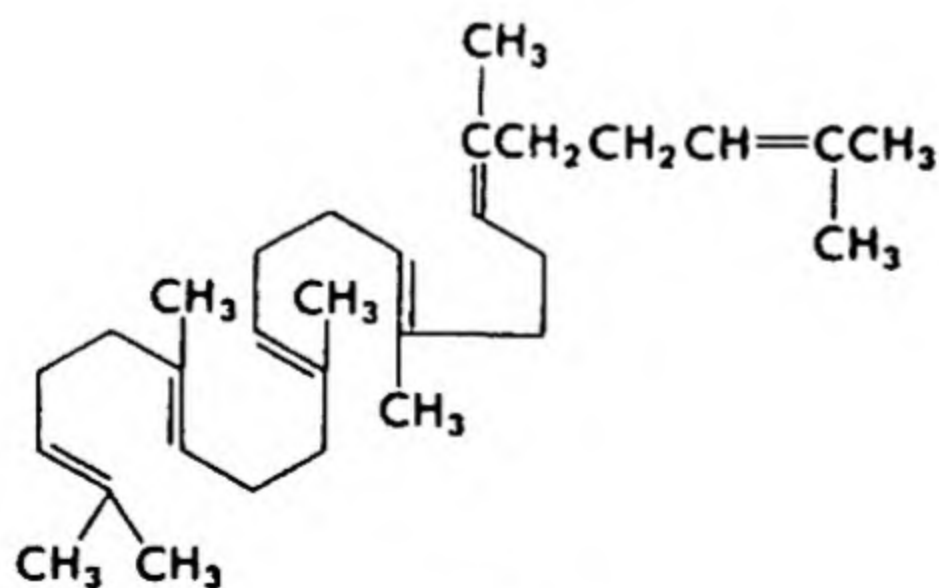
Closely related, biochemically, to terpenes are the steroids, polycyclic compounds which perform a variety of important biochemical functions. The relationship between terpenes and steroids is readily apparent upon comparing the formulas of lanosterol, a triterpene, and cholesterol, a steroid. The triterpene, squalene, is a biochemical intermediate in the



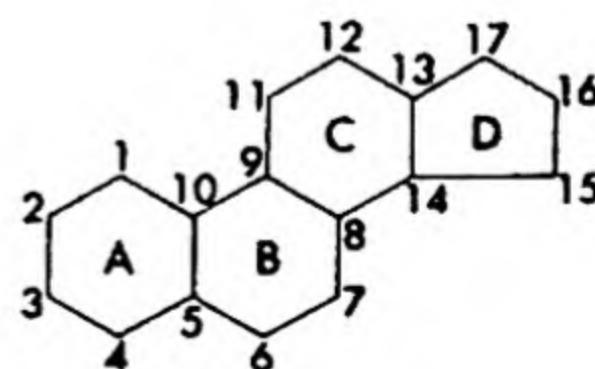
lanosterol



cholesterol

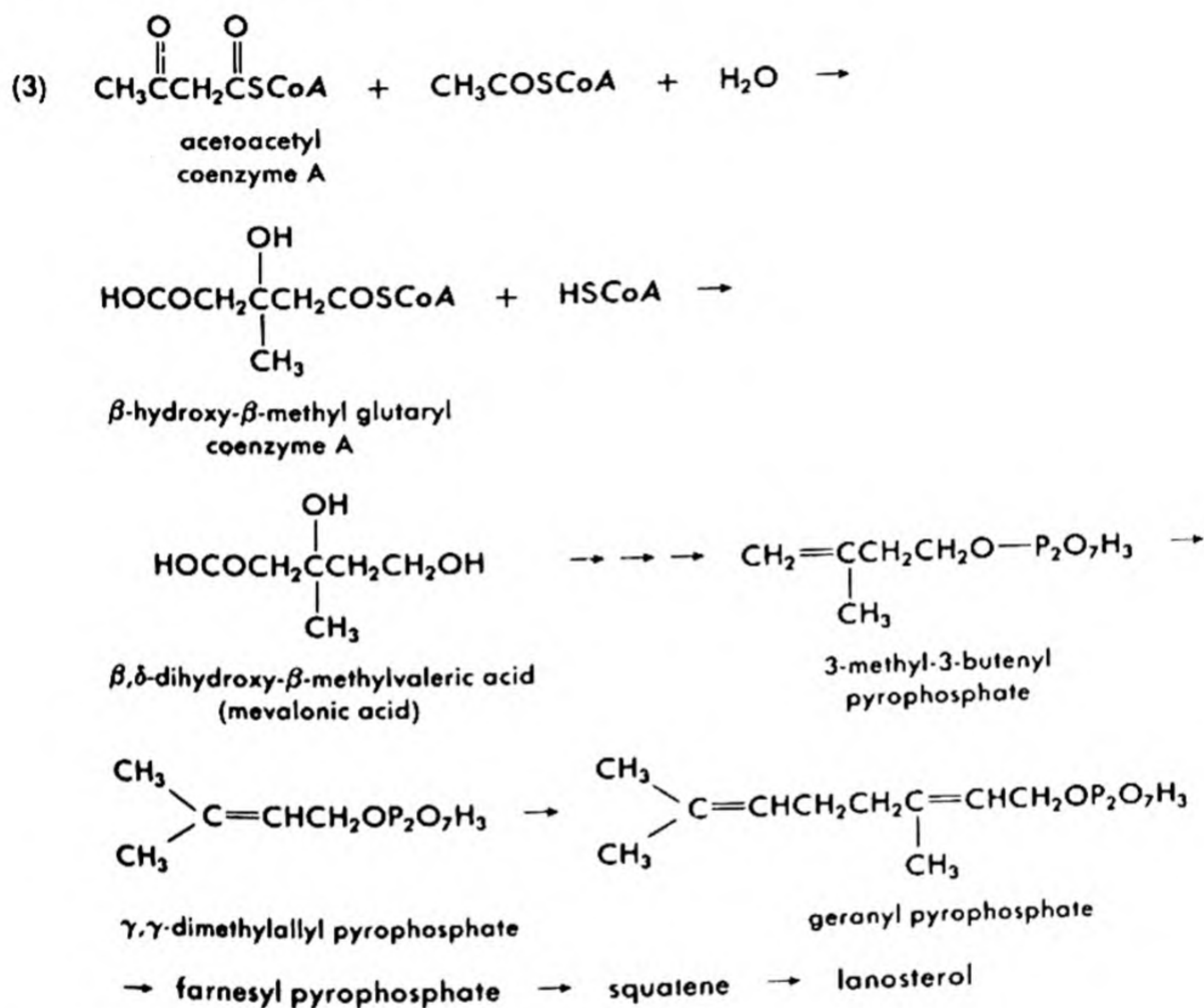


squalene



perhydrocyclopentanophenanthrene

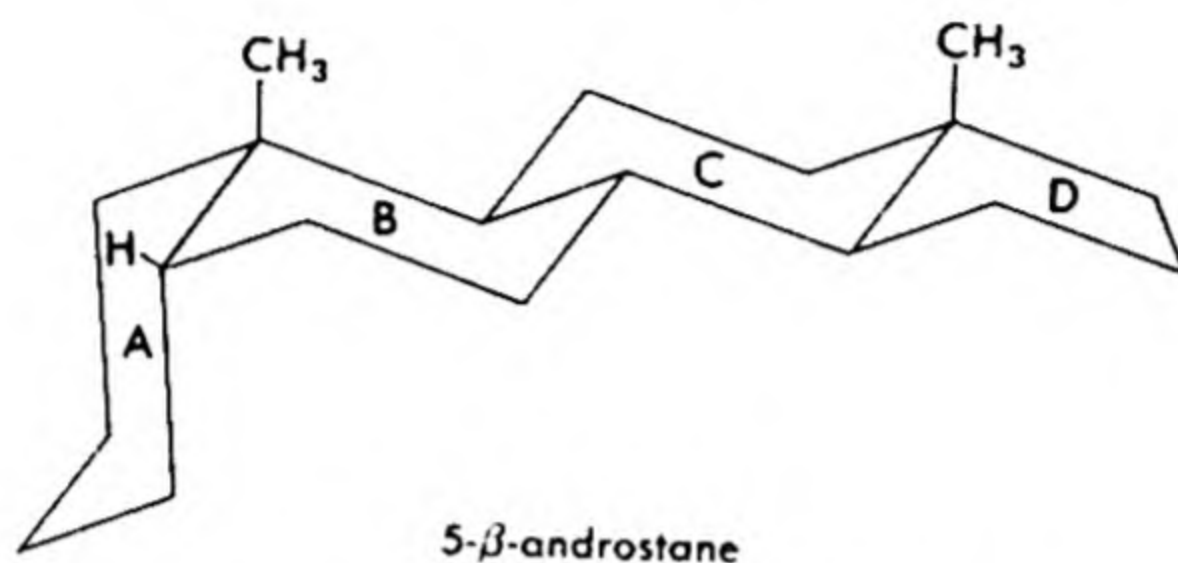
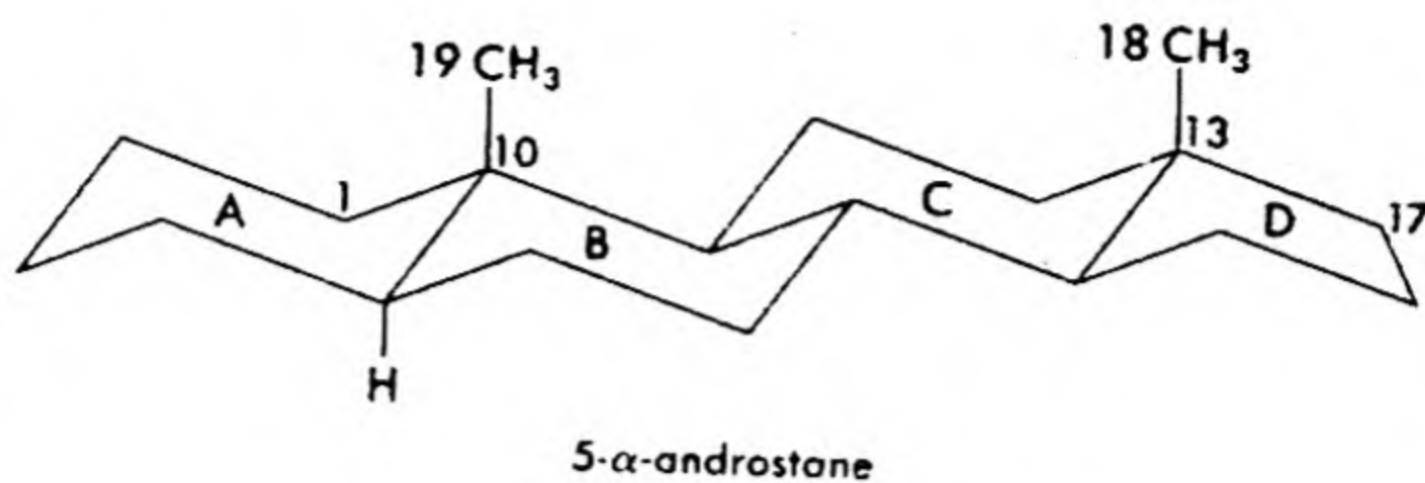
synthesis of lanosterol, cholesterol, and probably other steroids from acetate. The biochemical sequence involved in the biogenesis of lanosterol is now known. The intermediates are shown in outline (3). All of these are enzymatic reactions; many involve ATP or oxidation-reduction coenzymes. For the formation of acetyl coenzyme A and acetoacetyl coenzyme A see §40-1F.



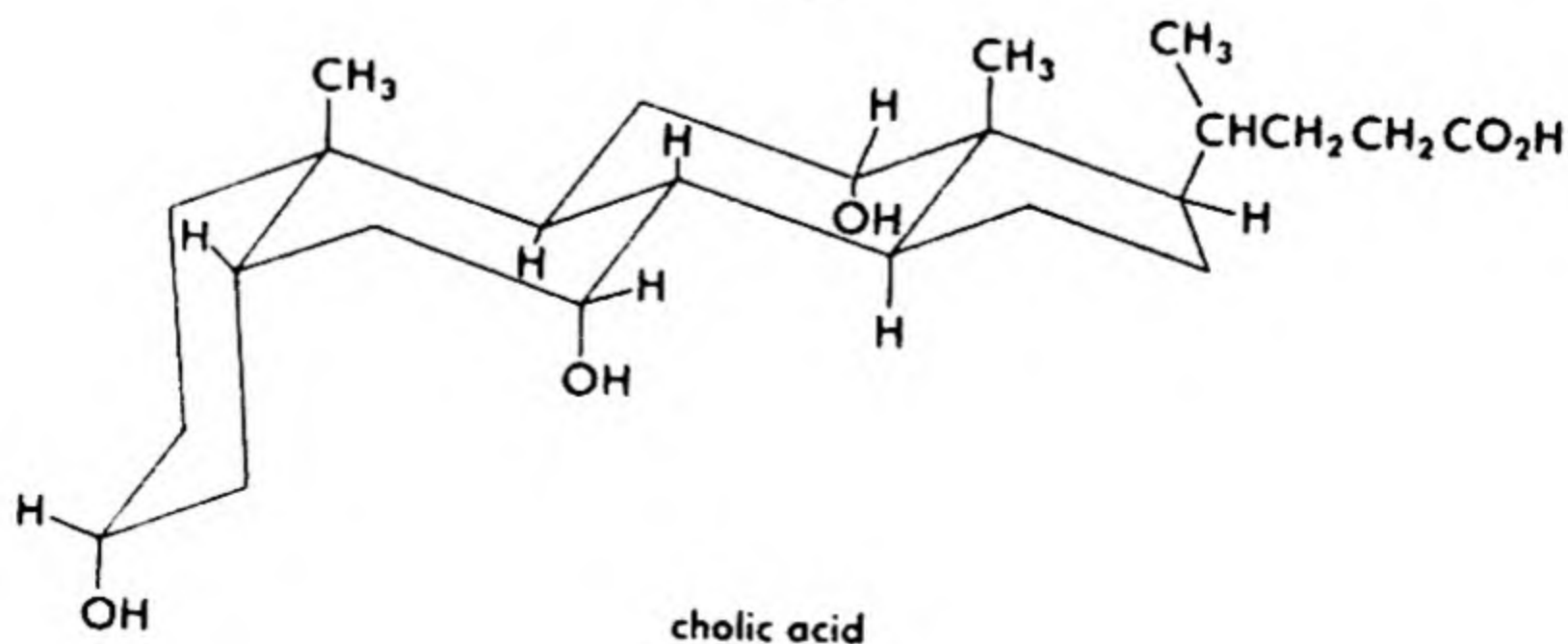
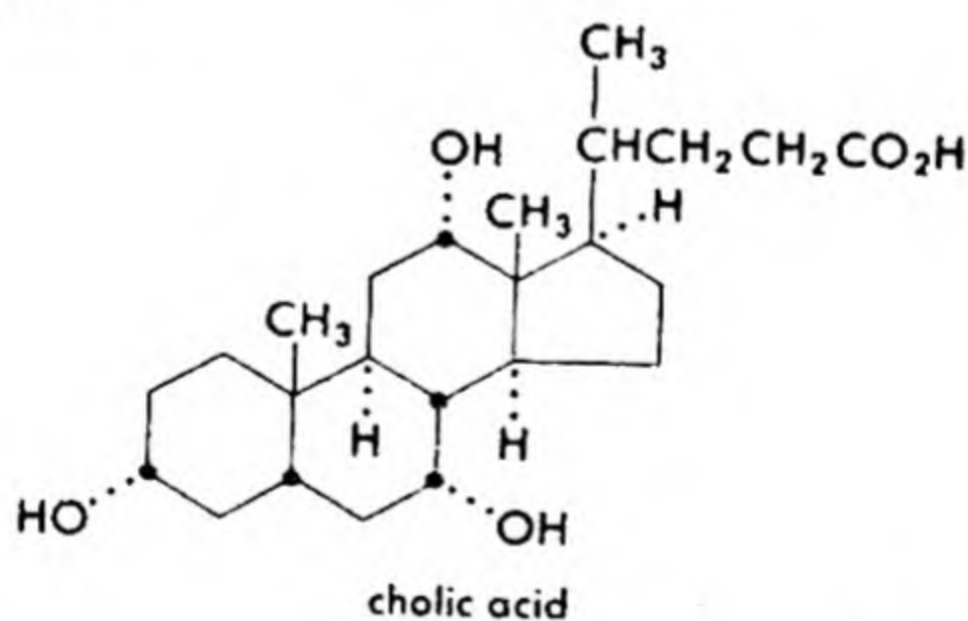
A. Classification and Structure of Steroids

Steroids can be subclassified on the basis of their functional groups such as sterols, which are alcohols (e.g., cholesterol). Such classification becomes unnecessarily complicated in the cases of polyfunctional steroids, which tend to be classified on the basis of biological function. All have in common the steroid ring system perhydropentanophenanthrene. In addition, there are the characteristic angular methyl groups at positions 10 (19-methyl) and 13 (18-methyl), and a chain of varying length at position 17 (numbered from 20).

The stereochemistry of steroids is of interest, in that two classes are recognized on the basis of ring junctures at positions 5 and 10. When the ring juncture between rings A and B is *trans*, the ring system belongs to

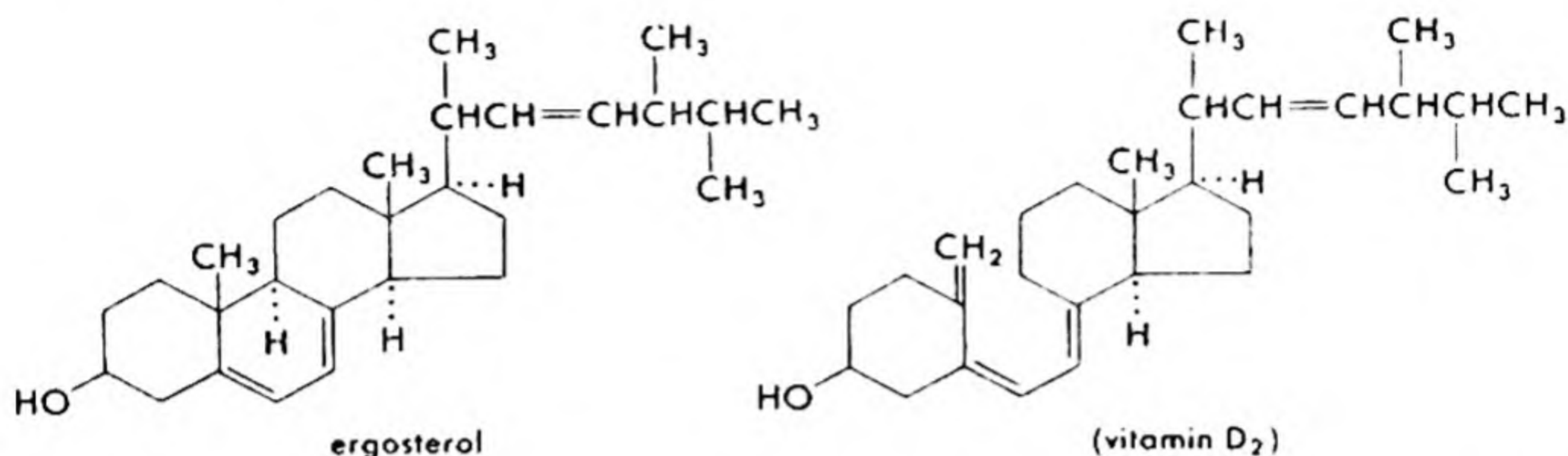


that called 5 α -androstane. When this juncture is *cis*, the ring system is that called 5 β -androstane. The α and β designations indicate arrangement up and down from the plane of the ring, respectively. Other representations for up and down orientation are often used; for example, a dot on a ring means a hydrogen atom up from the ring and a dotted line means the attached group points down. Thus, the salient features of cholic acid are represented in a conventionalized formula and in the equivalent conformational formula.



B. Some Important Steroids

Cholesterol is the most abundant animal sterol. In plants, ergosterol is the principal sterol. Ergosterol is also important as a source of vitamin D₂ for animals (see §26-9).

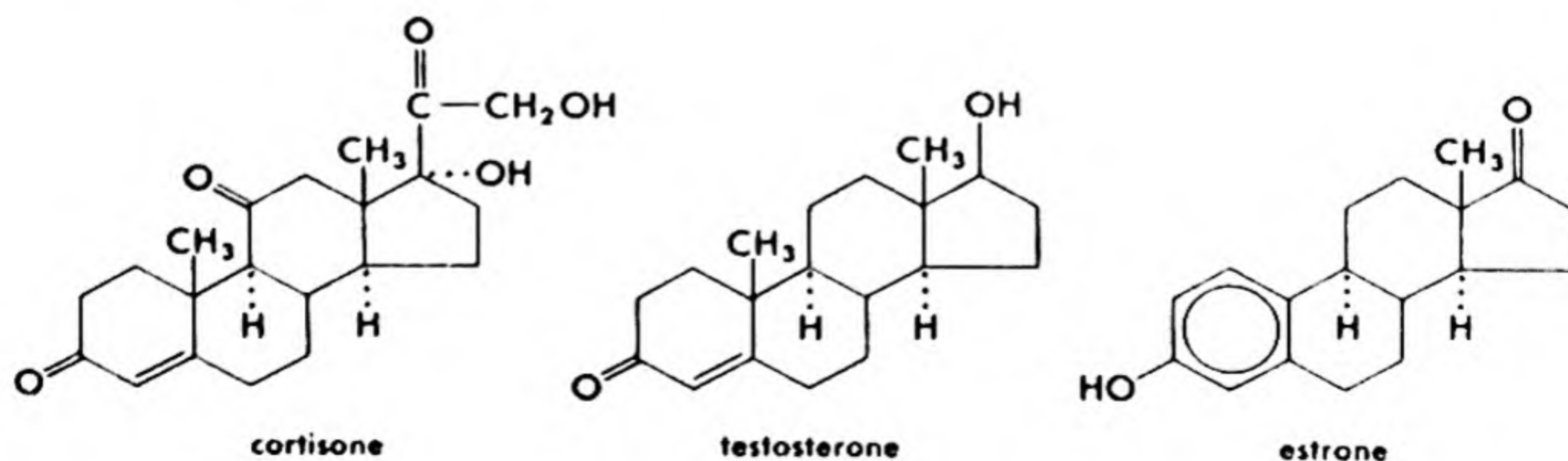


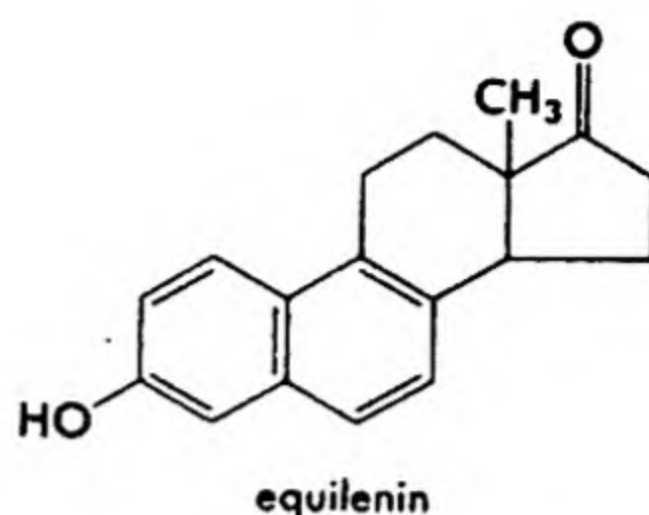
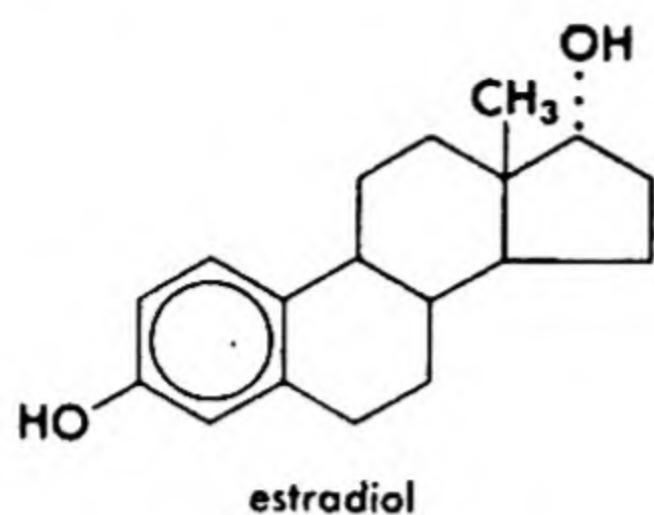
The bile salts, salts of taurocholic acid and glycocholic acid, emulsify food fats and aid their transport across intestinal villi to the lymphatic system. In these acids, the RCO groups shown in the formulas are choloyl groups (acyl radicals from cholic acid).



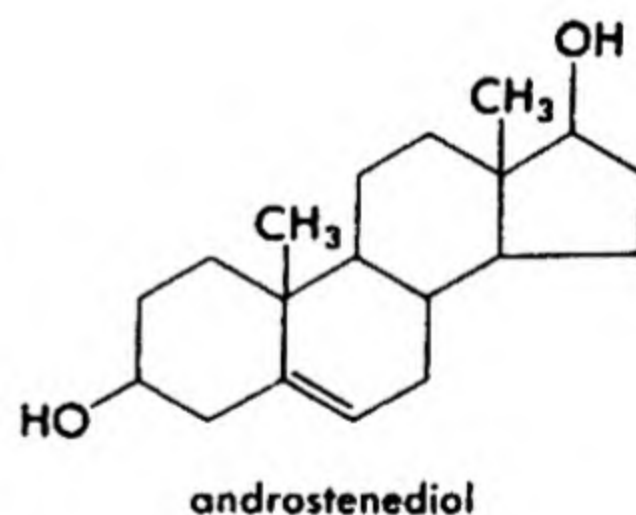
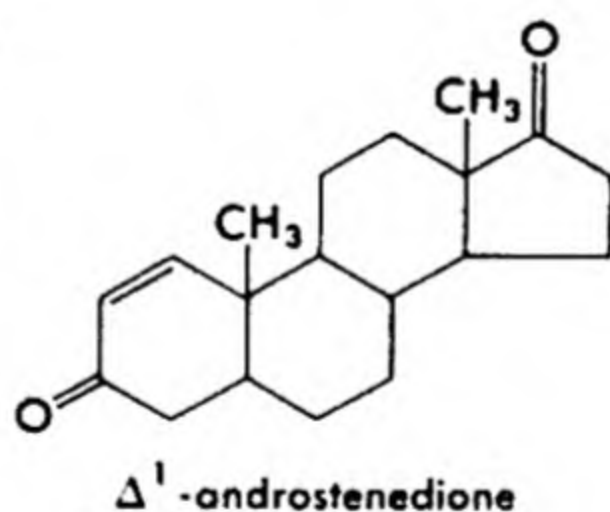
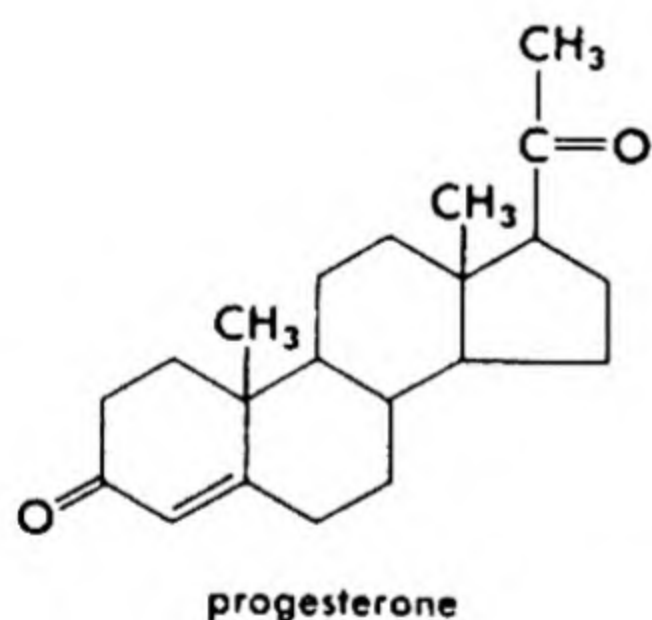
A number of hormones are steroids. Hormones are metabolic regulators; their function is to control and integrate biochemical processes through a complex system of checks and balances. Hormones are produced in the endocrine glands.

The adrenal cortex produces the important steroid cortisone. This hormone balances against insulin in hexose utilization and storage. Medicinally, it has been used to reduce inflammation and irritation in joints (arthritic or stress-induced).



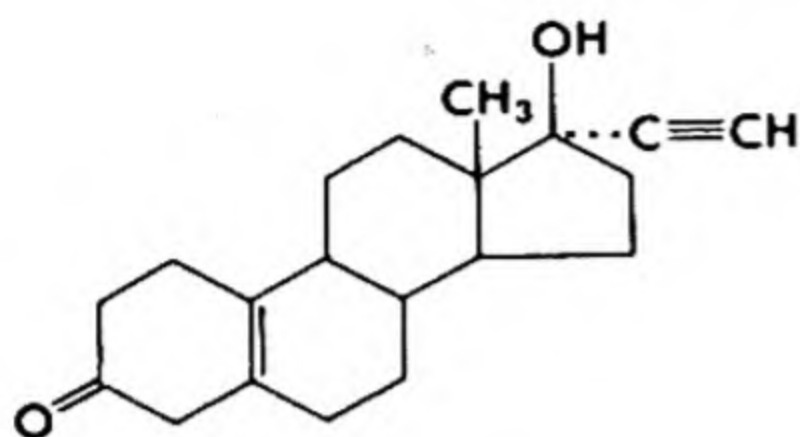


The sex hormones are steroids produced in the adrenal cortex and in the gonads (testes, ovaries). Their function is to regulate sexual function and secondary sex characteristics (those apparent differences associated with the sexes, such as skin texture, hair, distribution of fatty tissue). Those hormones associated with male characteristics are *androgens*, such as testosterone and its C_{17} oxidation derivative, androstenedione. Those hormones associated with female characteristics are *estrogens*, such as estrone, estradiol, and equilenin. Note that the estrogens have an aromatic A ring and that the methyl group at C_{10} is therefore not present. Progesterone is associated both with the menstrual cycle and with pregnancy. Certain "synthetic hormones" (more properly, steroid drugs) also have androgenic and estrogenic activity. Δ^1 -Androstenedione is a synthetic estrogen (despite its name), whereas androstenediol shows both

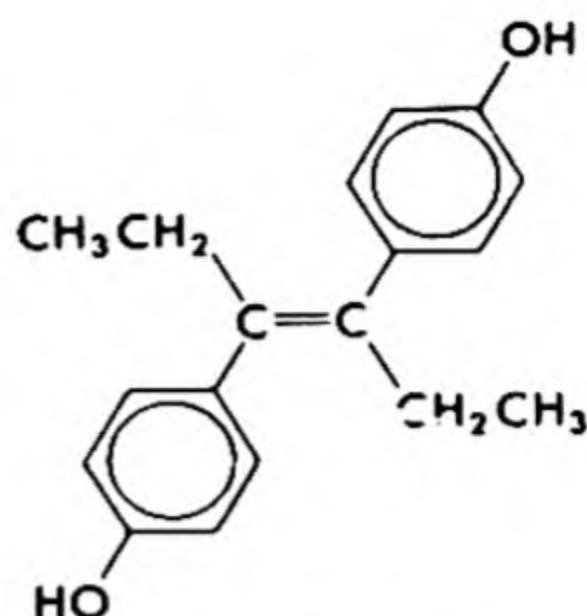


estrogenic and androgenic activity. A comparison of the formulas of these sex hormones shows significant variation in biological activity with but slight variation in structure. Synthetic compounds without C_{19} also show biological activity. Thus norethynodrel has progesterone activity and is used both to maintain a pregnancy in habitual aborters and to prevent ovulation.

It is of interest that a nonsteroid drug, diethylstilbestrol, is a potent estrogen, which illustrates the fact that structure-activity relationships in biologically active materials are not simple.



norethynodrel



diethylstilbestrol

SUPPLEMENTARY READINGS

- Eastman, R. H., and C. R. Noller, "The Terpenes" in H. Gilman, *Organic Chemistry, An Advanced Treatise*, Vol. IV, Wiley, New York, 1953, pp. 581-722.
- Eick, G. H., "Tall Oil and Terpene Derivatives," *J. Chem. Educ.* **34**, 613-614 (1957).
- Fieser, L. F., and M. Fieser, *Steroids*, Reinhold, New York, 1959, Chapter 1, "Orienting Survey," Chapter 5, "Physical Methods of Characterization"; other chapters may be selected on basis of interest.
- de Mayo, P., *The Higher Terpenoids*, Interscience, New York, 1959.
- de Mayo, P., *Mono- and Sesquiterpenoids*, Interscience, New York, 1959.
- Pinder, A., *The Chemistry of Terpenes*, Wiley, New York, 1961.
- Richards, J. H., and J. B. Hendrickson, *The Biosynthesis of Steroids, Terpenes and Acetogenins*, Benjamin, New York, 1964.
- Shoppee, C. W., *Chemistry of the Steroids*, 2nd Ed., Butterworths, London, 1964.

QUESTIONS AND PROBLEMS

1. Give an explanation, illustration, or definition to show clearly what is meant by each of the following terms. Accompany diagrams with verbal explanation.

- | | |
|------------------|----------------------------------|
| a. androgen | f. polyterpene |
| b. azulene | g. sesquiterpene |
| c. estrogen | h. terpene |
| d. hormone | i. Wagner-Meerwein rearrangement |
| e. isoprene rule | |

2. Write *full* structural formulas for the following terpenes. Classify them on the basis of their carbon skeletons, both as to number and as to arrangement of carbon atoms.

- | | |
|-----------------|---------------------|
| a. abietic acid | f. menthol |
| b. cadinene | g. α -pinene |
| c. camphor | h. selinene |
| d. geranial | i. squalene |
| e. limonene | j. zeaxanthin |

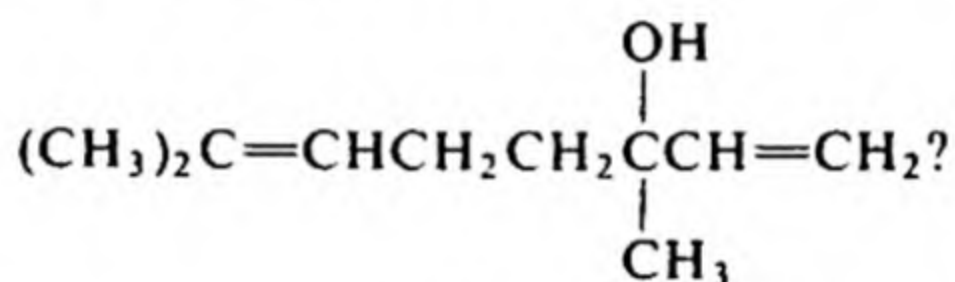
3. Show how camphor might be synthesized from acetone and ethanol. Bear in mind the possibilities of rearrangements. Indicate necessary inorganic reagents and special conditions.

4. Cite two structural features in which estrone and estradiol differ significantly from other sex hormones. In what way is stilbestrol related to the structures of these estrogens? Write formulas which show the analogous structural features by similar orientation of groups.

5. Myrcene has an intense ultraviolet absorption at 2245 Å ($\epsilon = 14,600$). Ocimene has similar absorption. Explain.

6. When ocimene is heated, it is converted to an isomer called alloöcimene. This has an intense absorption at 2750 Å. Ozonolysis of alloöcimene, followed by zinc reduction of the ozonide, gives acetone and acetaldehyde. Write a suitable structure for alloöcimene.

7. How would the infrared and nuclear magnetic resonance spectra of geraniol differ from those of its allylic isomer, linaloöl,



How would you interconvert geraniol and linaloöl? Write a mechanism for this interconversion.

8. Give a reasonable reaction path for the conversion of citral to cyclocitral.

9. There are eight stereoisomers with the menthol structure. Draw their conformational formulas.

10. How would one distinguish zingiberene from bisabolene by physical methods? By chemical methods?

11. Assuming that biosynthetic processes are mechanistically similar to acid-catalyzed reactions, show how farnesol can be transformed to bisabolene and substances with the same carbon skeletons as cadinene, selinene, and eremophilone.

12. How can one distinguish α , β , and γ -terpinenes? β -Terpinene is 1-isopropyl-4-methylidenecyclohexene. γ -Terpinene is 1-methyl-4-isopropyl-1,4-cyclohexadiene.

13. Show how the interconversion of γ,γ -dimethylallyl pyrophosphate to farnesyl pyrophosphate and of squalene to the ring system involved in lanosterol can be accommodated to carbonium ion mechanisms.

42

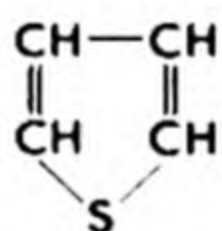
Heterocycles

42-1 SIMPLE AND COMMON FUSED HETEROCYCLES AND THEIR DERIVATIVES

Heterocycles are cyclic compounds which have more than one kind of atom in the ring. (Gk., *heteros*, other, + cycle). Some heterocycles, such as cyclic anhydrides and imides, lactides, lactones and lactams, and cyclic acetal forms of carbohydrates, have already been discussed.

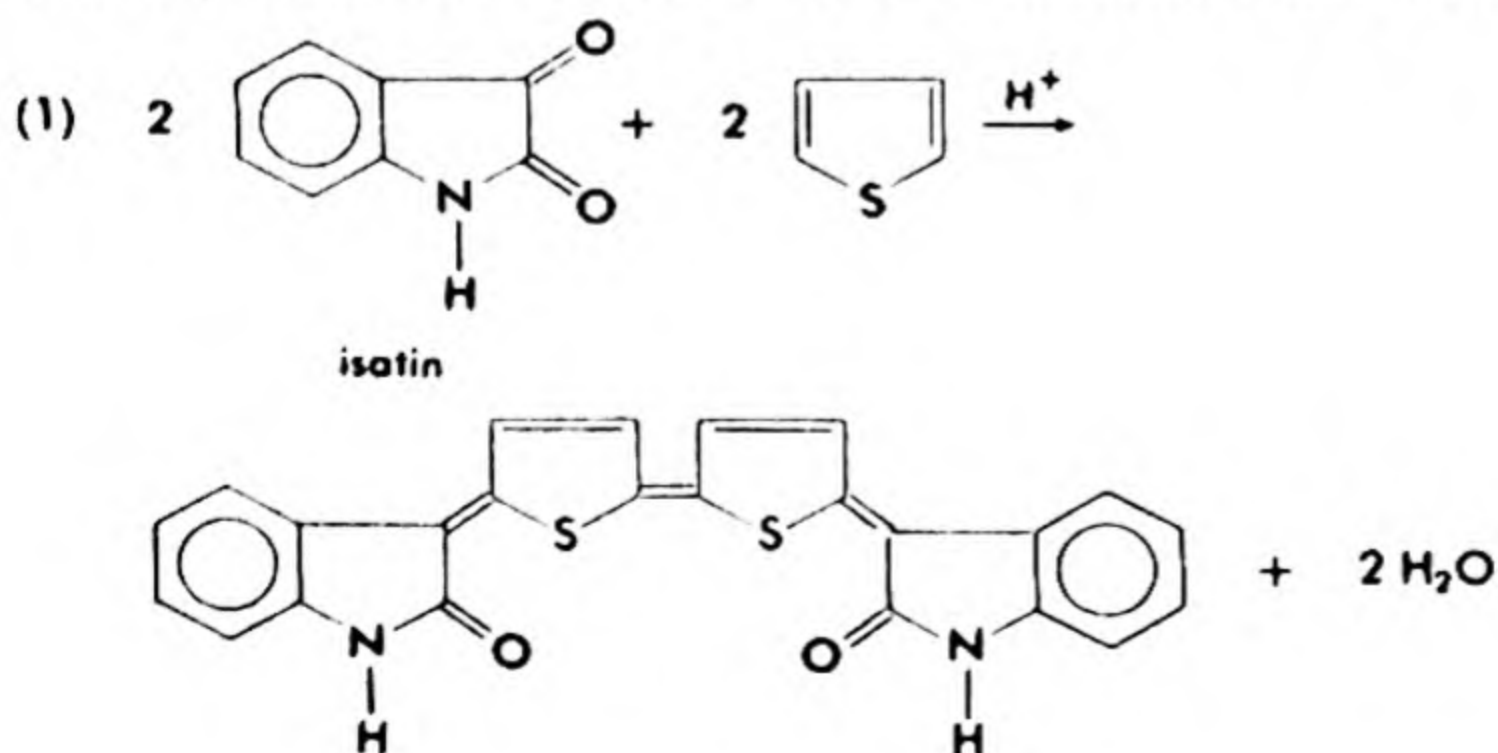
A. Occurrence

Vast numbers of heterocycles are of great importance to life. Some are the amino acids proline, hydroxyproline, and tryptophan and the co-enzymes considered in Chapter 38 and others considered later in this chapter.



thiophene

The occurrence of thiophene in the benzene fraction of coal tar was discovered by Victor Meyer in dramatic fashion. Adolf von Baeyer had developed the indophenin test, which he believed was specific for benzene. The liquid is shaken with concentrated sulfuric acid and a little isatin.



Meyer, in a lecture demonstration and using a sample of benzene prepared from sodium benzoate, failed to get the expected blue color. Meyer's later investigation revealed that thiophene present in small amounts in the coal tar fraction, not benzene, was responsible for the test. The reaction is a condensation between thiophene and the isatin (eq. 1). Other α,β -diketones also condense with thiophene.

A number of heterocyclic compounds not obtainable as such from natural sources are readily prepared from naturally occurring compounds.

B. Nomenclature

Like carbocyclic compounds, heterocycles exist in both simple ring systems and condensed ring systems. The IUPAC system provides suffixes for ring size and degree of unsaturation for simple rings, and prefixes to indicate the number and kind of hetero atoms. Table 42-1 gives the suffixes for rings containing up to ten atoms. Prefixes to designate hetero atoms are ox(a)-, —O—; thi(a)-, —S—; az(a)-, —N=; selen(a)-, phosph(a)-, etc. The usual numerical prefixes indicate multiplicity of hetero atoms. Examples of common and systematic nomenclature of the more important simple ring systems are given in Tables 42-2 and 42-3. Ring formulas in this chapter are written in line abbreviations. All double or triple bonds are shown.






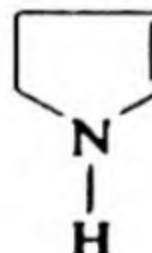
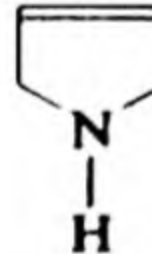
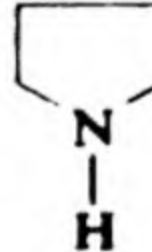
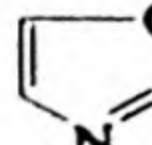
TABLE 42-1. Suffixes of Simple Heterocycles

Total Atoms in Ring	Without Nitrogen			With Nitrogen		
	Most Un-saturated	One Double Bond ^a	Saturated	Most Un-saturated	One Double Bond ^a	Saturated ^a
3	—	-irene	-irane	—	-rine	-iridine
4	-ete	-etene	-etane	-ete	-etine	-etidine
5	-ole	-olene	-olane	-ole	-oline	-olidine
6	-in		-inane	-ine		
			or -ane			
7	-epin		-epane	-epine		
8	-ocin		-ocane	-ocine		
9	-onin		-onane	-onine		
10	-ecin		-ecane	-ecine		

^a For ring sizes of six or more atoms, prefixes dihydro-, tetrahydro-, etc. are placed before the name of the most unsaturated forms. The prefix for the saturated nitrogen-containing heterocycle is perhydro-.

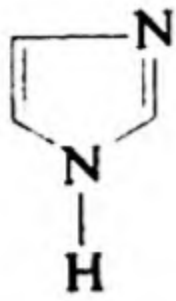
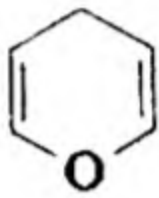
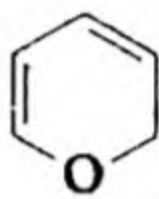
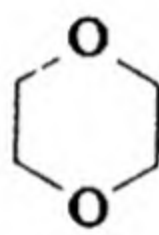
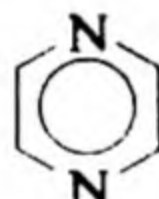

Condensed ring systems and simple ring systems of more than ten ring atoms are to be named, according to IUPAC recommendation, by using the hetero atom prefixes with position numbers on the names of the corresponding carbocycles. Examples are given in Table 42-3.

TABLE 42-2. Nomenclature of Simple Heterocycles

Structure	Common Name	IUPAC Name
	Ethylene oxide	Oxirane Epoxyethane ^a
	Ethylenimine	Aziridine
	Urete	1,3-Diazete
	Tetrahydrofuran	Oxolane
	Thiophene	Thiole
	β -Pyrroline	Δ^2 -Azoline
	γ -Pyrroline	Δ^3 -Azoline
	Pyrrolidine	Azolidine
	Oxazole	1,3-Oxazole

^aThis alternative is preferred when the name is simplified by its use.

TABLE 42-2. Nomenclature of Simple Heterocycles (cont.)

Structure	Common Name	IUPAC Name
	Imidazole	1,3-Diazole
	γ -Pyran	1,4H-Oxin
	α -Pyran	1,2H-Oxin
	<i>p</i> -Dioxane, Diethylene dioxide	1,4-Dioxane
	Pyrazine	1,4-Diazine
	Pyridazine	1,2-Diazine

American usage (Chemical Abstracts) differs from the IUPAC recommendation. In the C.A. system, fused ring systems are named from their simple components. The added rings are denoted by prefixes such as *benzo-*, *naphtho-*, *pyrrolo-* (*azolo-*), and the like. *The Ring Index* (Appendix II, §II-2) gives details and many examples. (See also Table 42-3.)

C. Syntheses

Methods used to synthesize heterocyclic compounds can be classed under three main headings: ring formation by adaptations of conventional reactions, unconventional reactions applicable only to cyclization, and modification of already formed heterocycles.

TABLE 42-3. Nomenclature of Condensed Heterocycles

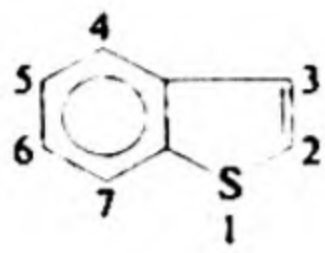
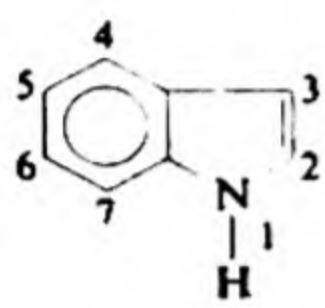
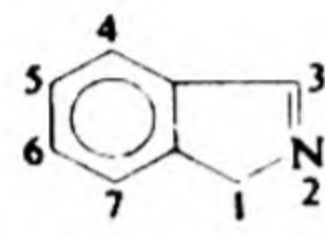
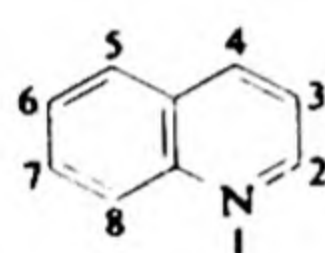
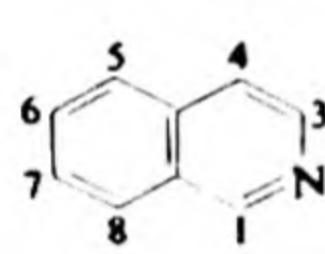
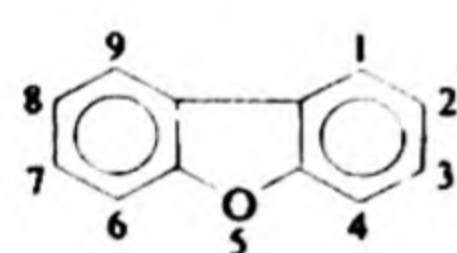
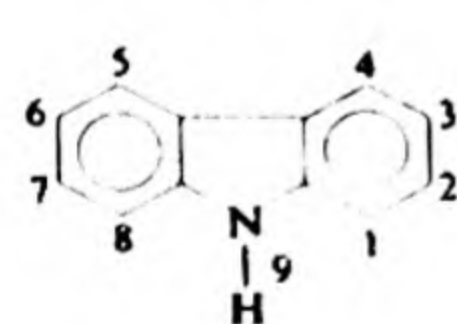
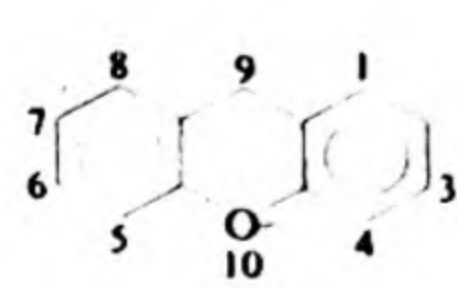
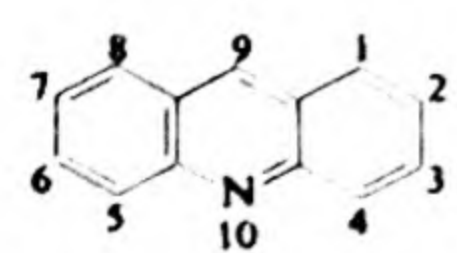
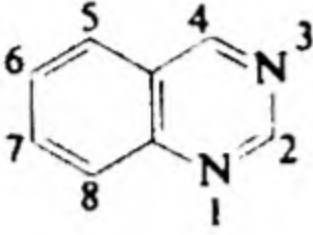
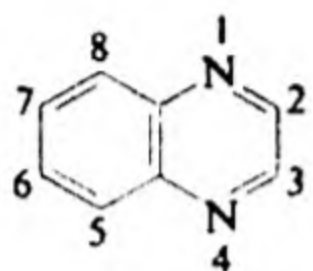
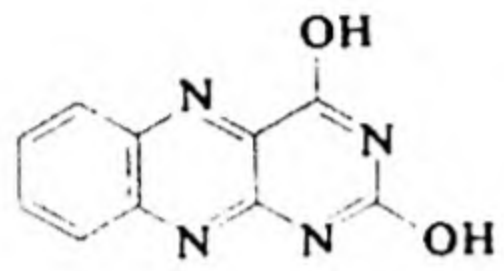
Structure	Common Name	IUPAC Name ^a	C.A. Systematic Name ^b
	Thianaphthene	1-Thiaindene	Benzo[b]thiophene
	Indole	1-Azindene	1-Benzo[b]pyrrole (Indole)
	Isoindole	2-Azindene	2-Benzo[c]pyrrole (Isoindole)
	Quinoline	1-Azanaphthalene	Benzo[b]pyridine (Quinoline)
	Isoquinoline	2-Azanaphthalene	Benzo[c]pyridine (Isoquinoline)
	Dibenzofuran		Dibenzo[b,d]furan
	Carbazole		Dibenzo[b,d]pyrrole (Carbazole)
	Xanthene	9,10-Dihydro- 10-oxanthracene	Dibenzo[b,e]pyran (Xanthene)
	Acridine	10-Azanthracene	Dibenzo[b,c]pyridine (Acridine)

TABLE 42-3. Nomenclature of Condensed Heterocycles (cont.)

Structure	Common Name	IUPAC Name ^a	C.A. Systematic Name ^b
	Quinazoline	1,3-Diazanaphthalene	Benzo[d]pyrimidine (Quinazoline)
	Quinoxaline	1,4-Diazanaphthalene	Benzo[b]pyrazine (Quinoxaline)
	Alloxazine	1,3,9,10-Tetra- zanthracene- 2,4-diol ^c	Pyrimido-(4,5-b)- quinoxaline-2,4-diol (Benzo[g]pteridine- 2,4(1H,3H)-dione)

^aSatisfactory systems for polycyclic heterocycles are yet to be developed by the IUPAC. Heteroatom substitution names break down where systematic names for parent hydrocarbons are lacking. The IUPAC now accepts the C.A. system as well as substitution names.

^bAlthough systematic names can be constructed as shown for the *Chemical Abstracts* system, the names actually indexed in *Chemical Abstracts* are those in parentheses, where these differ from the systematic names.

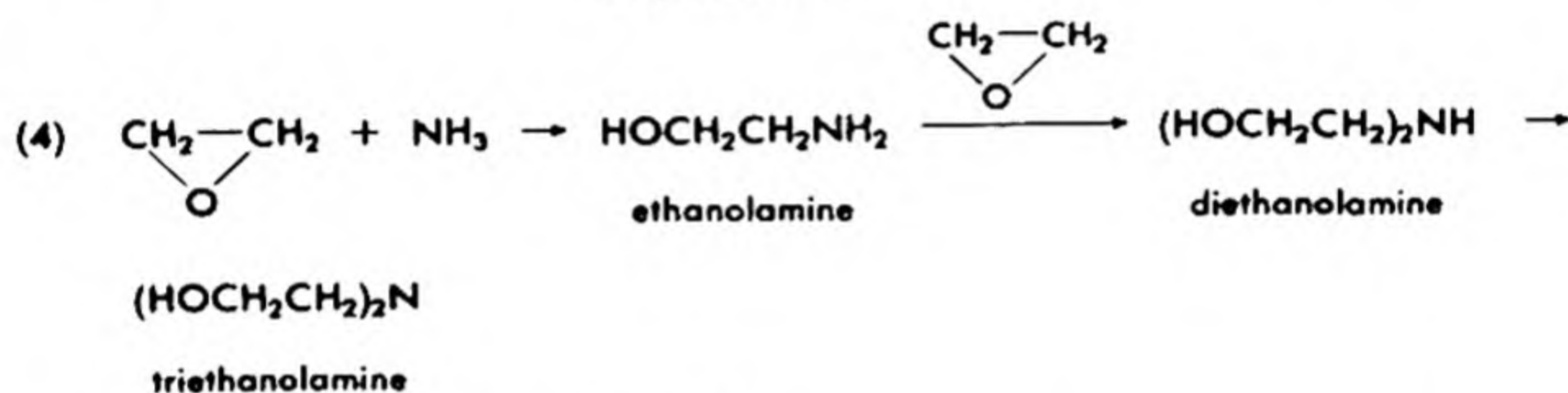
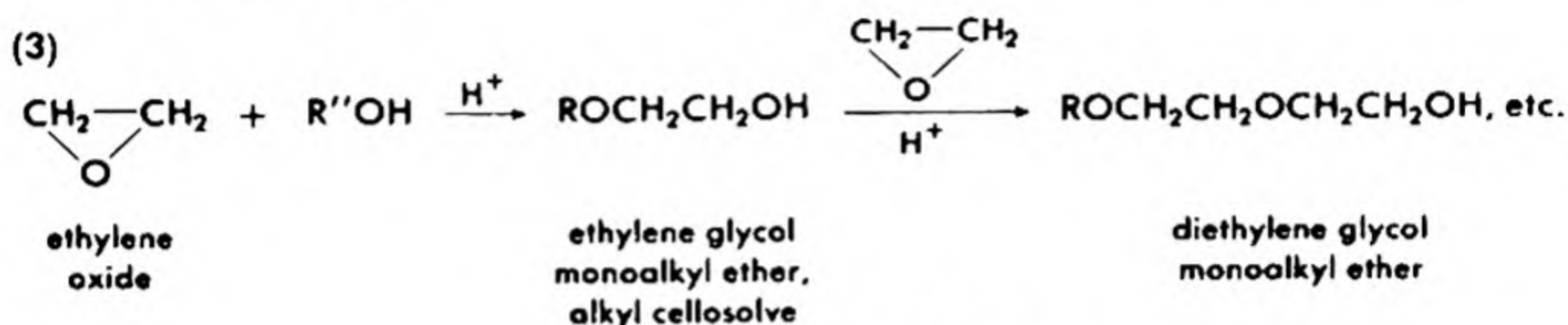
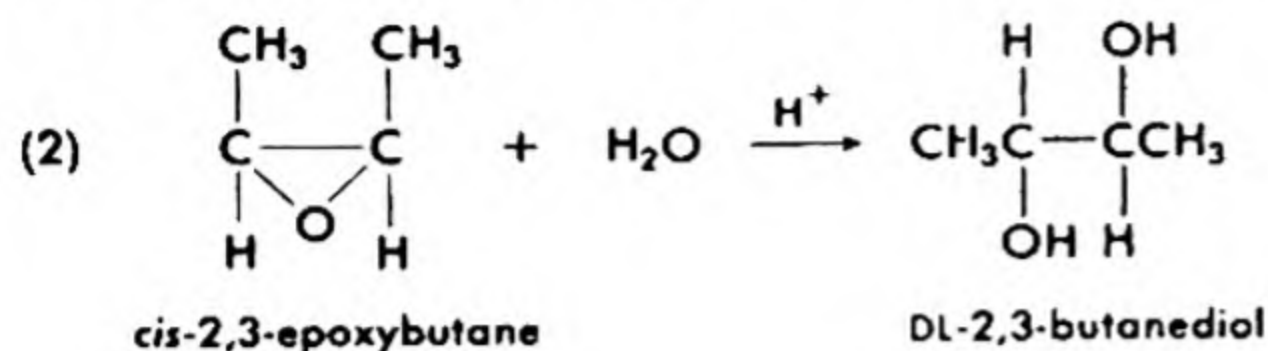
^cNumbering for the parent hydrocarbon differs from the C.A. numbering of the heterocycle, hence the IUPAC name is inconsistent with numbering in *The Ring Index*.

(1) *Cyclization by Modifications of Conventional Reactions.* The ease of formation of five- and six-membered rings has been pointed out on several occasions (§5-2C, §12-1C, §17-3F, §18-2D, §22-3 and Chapter 29). This tendency to ring formation is so great that rings can often be closed by reactions which would fail to form open chain compounds because of unfavorable point of equilibrium or prevalence of side reactions. The great ease of formation of cyclic anhydrides and imides is a familiar example. Thus, many ring closures involve conventional reactions preceded by enolization, or electrophilic reactions of very weak electrophiles, or nucleophilic reactions of very weak nucleophiles. Some examples are given in the discussion of specific systems. The field is much too broad even to be summarized in an introductory book.

D. Three-Membered Ring Systems

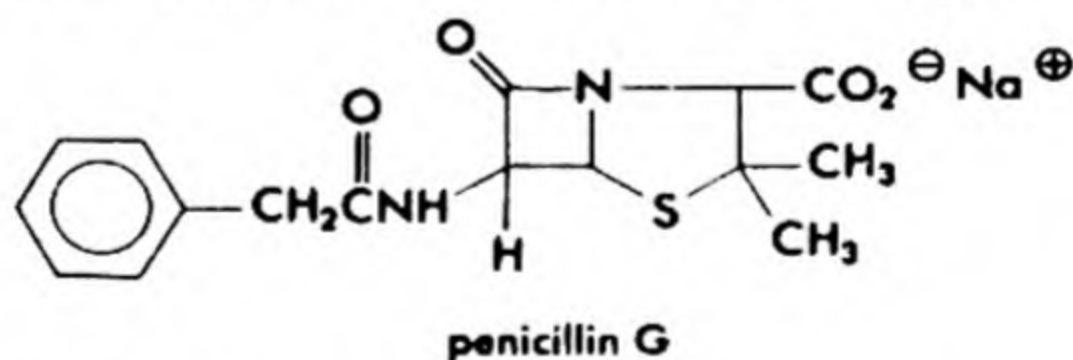
Epoxides (oxiranes) and alkyleneimines (aziridines) are the most important of the three-membered heterocycles. The epoxides are readily prepared by peroxidation reactions (§27-3A). Like small carbocycles, small heterocyclic rings are readily cleaved. Epoxy rings are readily

opened by acidic reagents and by nucleophiles. The ring openings are usually stereospecific and occur with inversion.



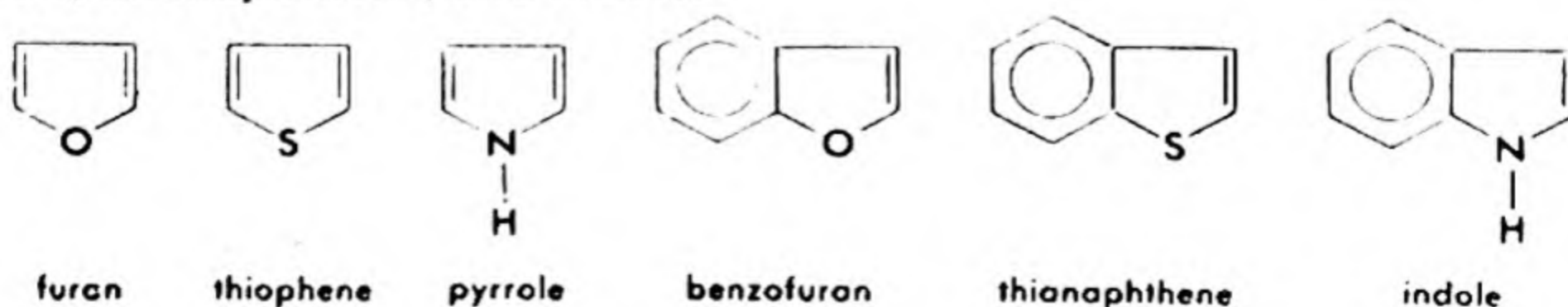
E. Four-Membered Ring Systems

The β -lactone system was pointed out as occurring in ketene dimer (§18-3). A similar ring occurs in the antibiotic family known as penicillins, such as benzylpenicillin (penicillin G); this is the β -lactam ring in the center of the compound. In general, the occurrence of four-membered heterocycles in nature is much rarer than that of larger rings.



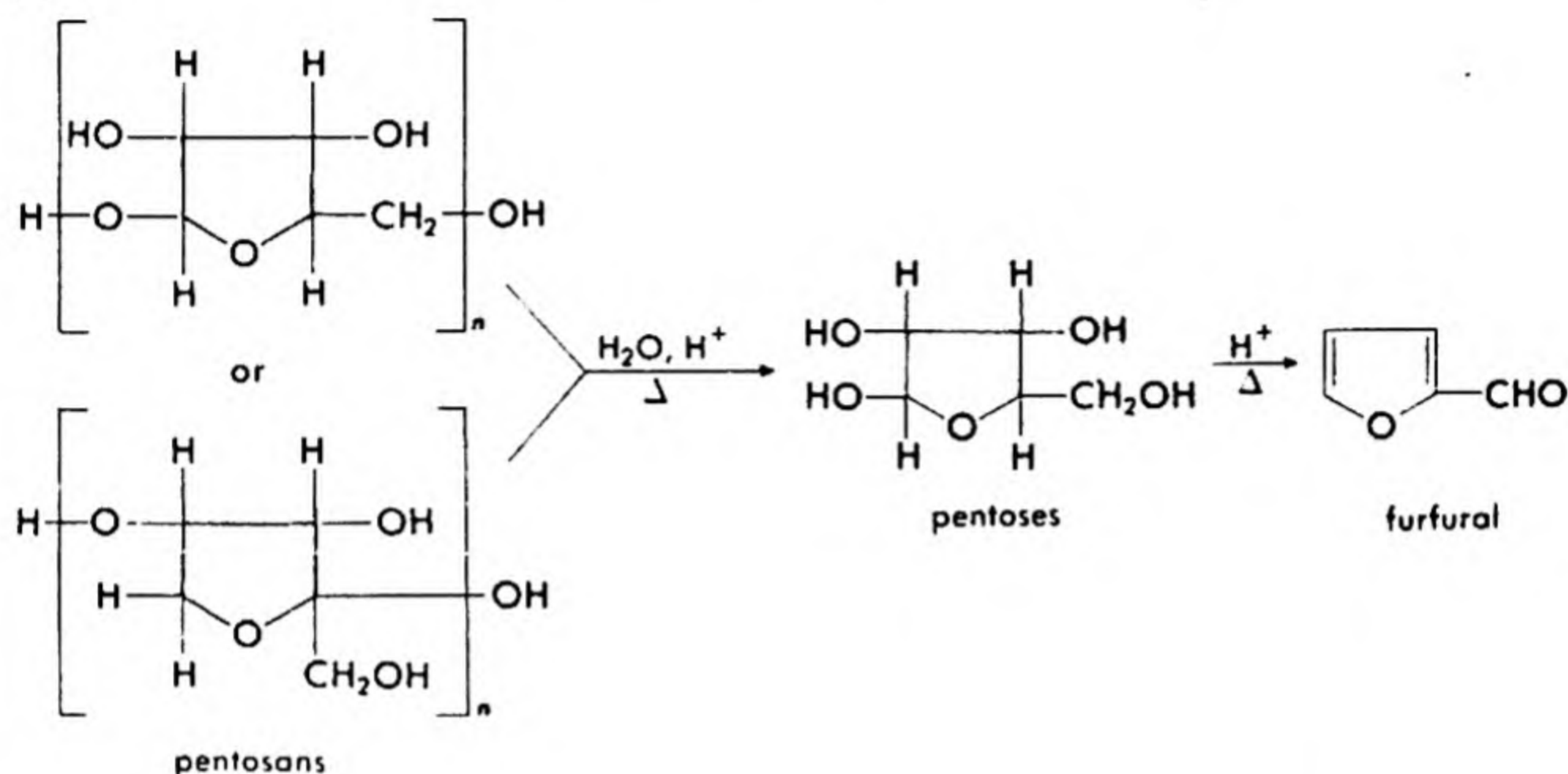
F. Five-Membered Ring Systems

Typical representatives of the five-membered ring systems are furan, thiophene, and pyrrole. Fused with benzene rings, these form benzofuran, thianaphthene, and indole.

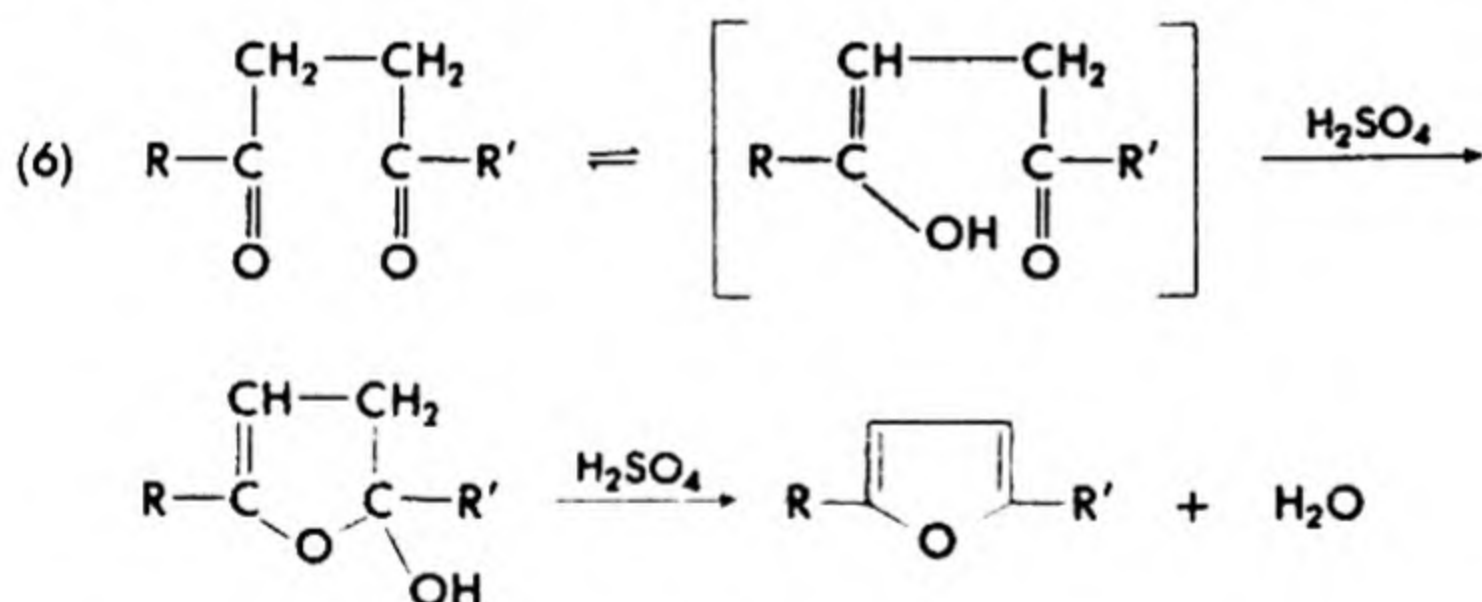


Furan derivatives are commercially important by-products of the grain industries. The most important of these is furfural. This compound is produced in commercial quantities by the action of strong acid on cereal wastes, such as oat hulls, rice hulls, and corn cobs (outline 5). The aldehyde is distilled out of the reaction mixture.

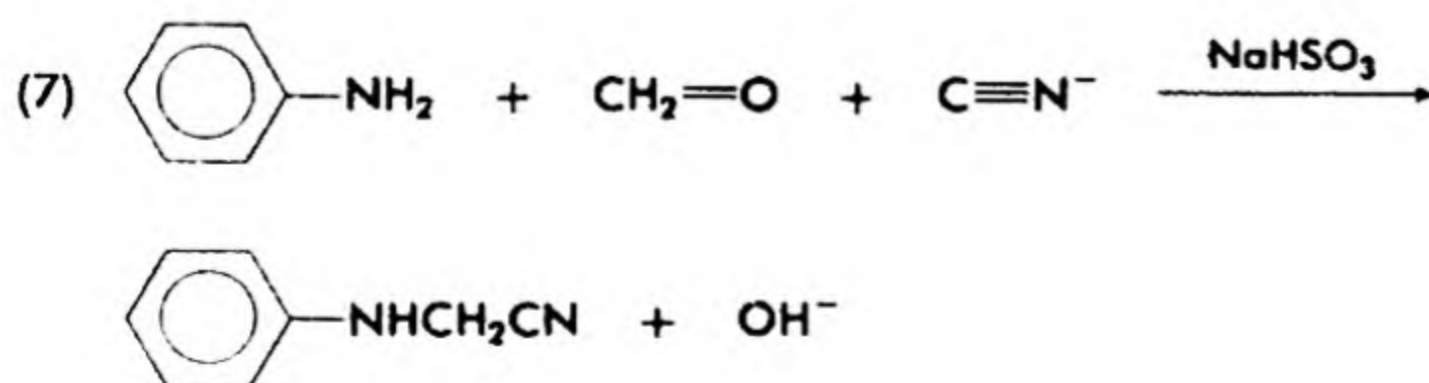
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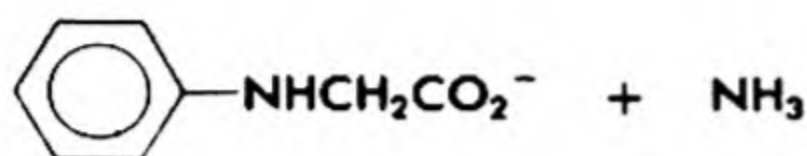
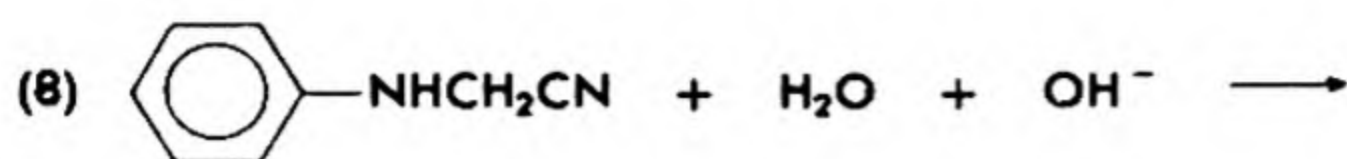


Substituted furans can be synthesized from diketones (outline 6).

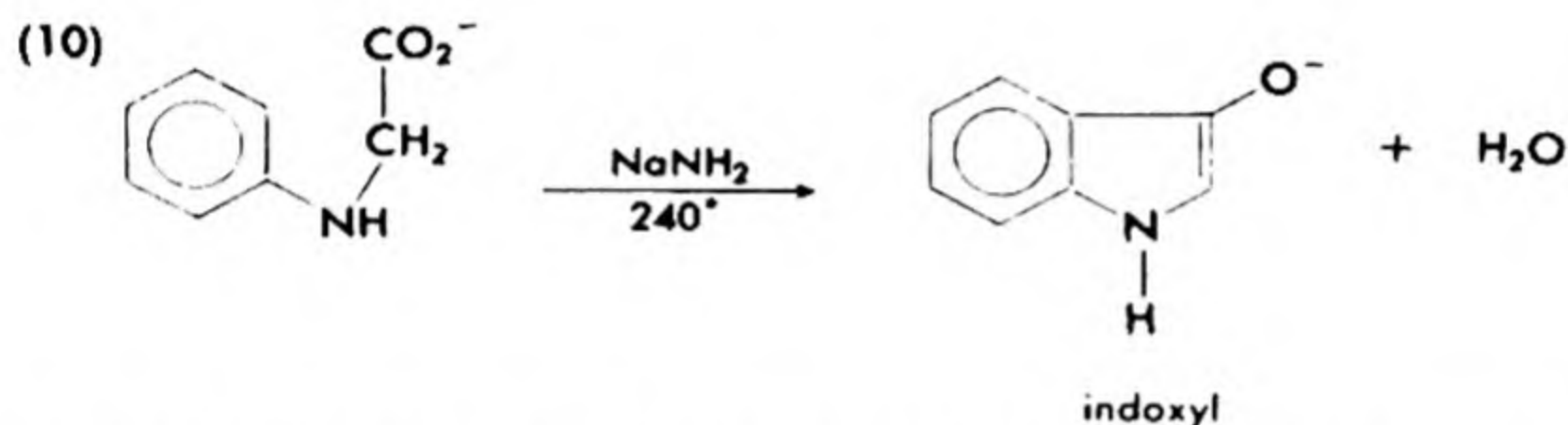


Pyrrole rings occur in a large number of biochemical products and intermediates, some of which are considered later. The dye, indigo, and its derivatives, isatin (§42-1A), and indoxyl, below, are several of commercial importance. Indoxyl is prepared from aniline by the sequence of steps illustrated in eqs. (7) through (10). Indoxyl is a water-soluble mate-

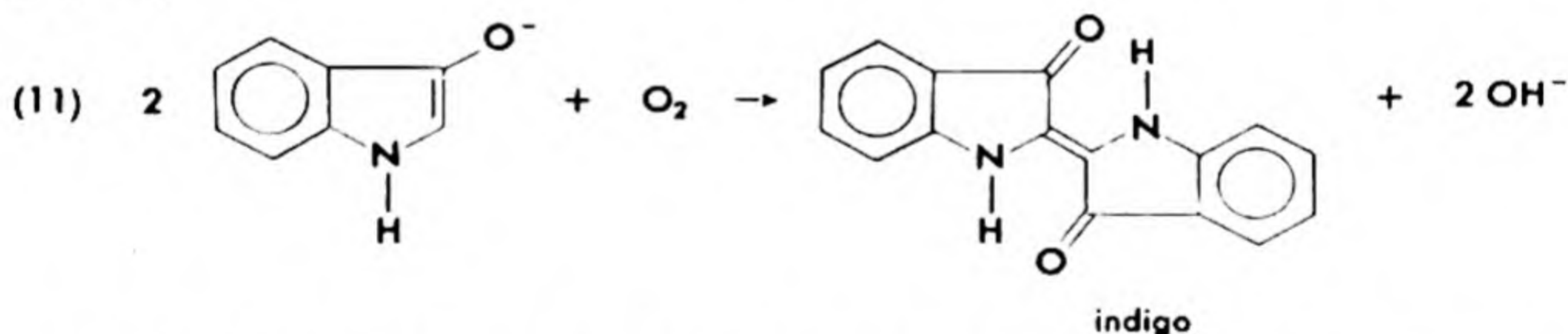




or



rial which is oxidized by air on a fabric to form the deep blue dye, indigo (eq. 11).



(1) *Physical Properties.* Physical properties of heterocycles are consistent with those of other compounds of similar polarity and planarity. Just as cycloalkanes and arenes have boiling points somewhat higher than those of open-chain isomers, heterocycles have boiling points somewhat higher than corresponding ethers, sulfides, imines, and secondary amines of open structure. Substituent groups on the rings have effects on physical properties similar to such groups in other organic combinations. Pyrrole has an unusually high boiling point.

(2) *Chemical Properties.* Furan, thiophene, pyrrole, and their benzo derivatives show chemical properties of typical aromatic systems, such as electrophilic substitution and high thermal stability. It may be recalled that aromaticity is associated with a closed six-electron π orbital system (§7-3A). It may also be noted that these five-membered rings contain, in

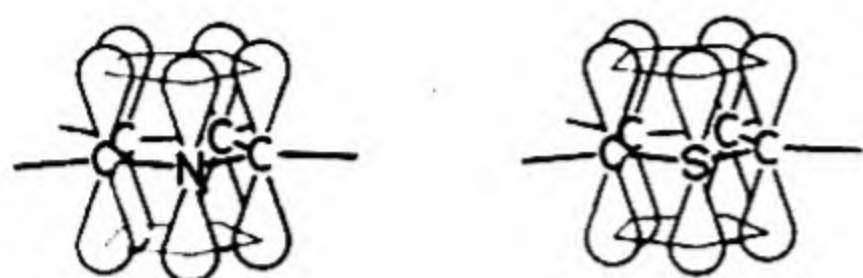
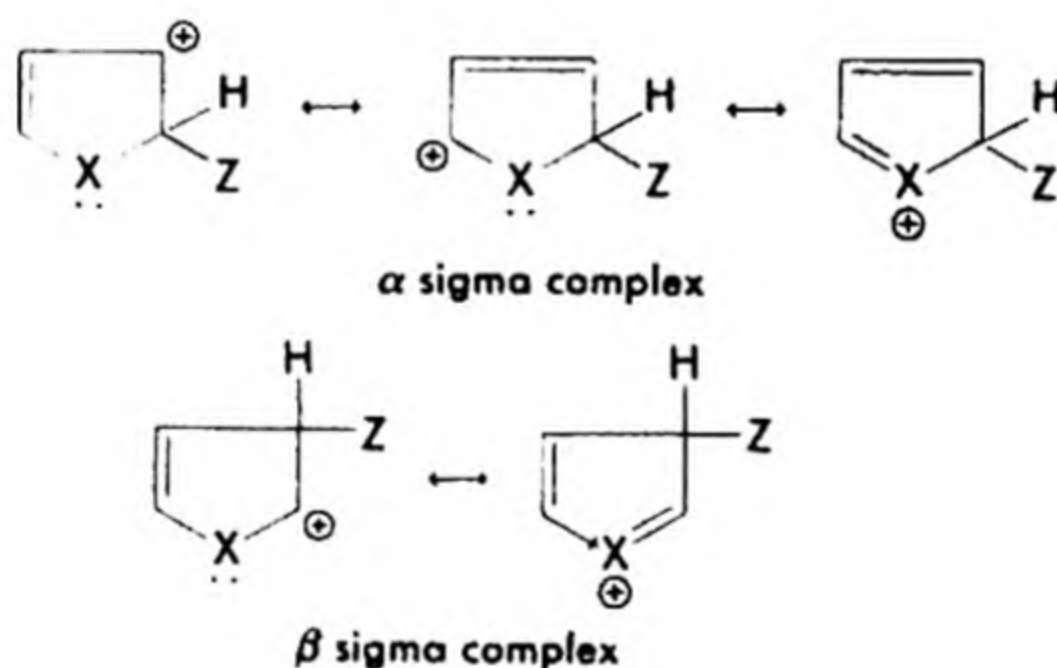


Fig. 42-1. MO Diagrams for Pyrrole and Thiophene.

addition to those electrons involved in annular and extraannular σ -orbitals, four p electrons from the carbon atoms and one unshared electron pair from the hetero atom. This makes available the required six electrons for an aromatic π -orbital system (Fig. 42-1).

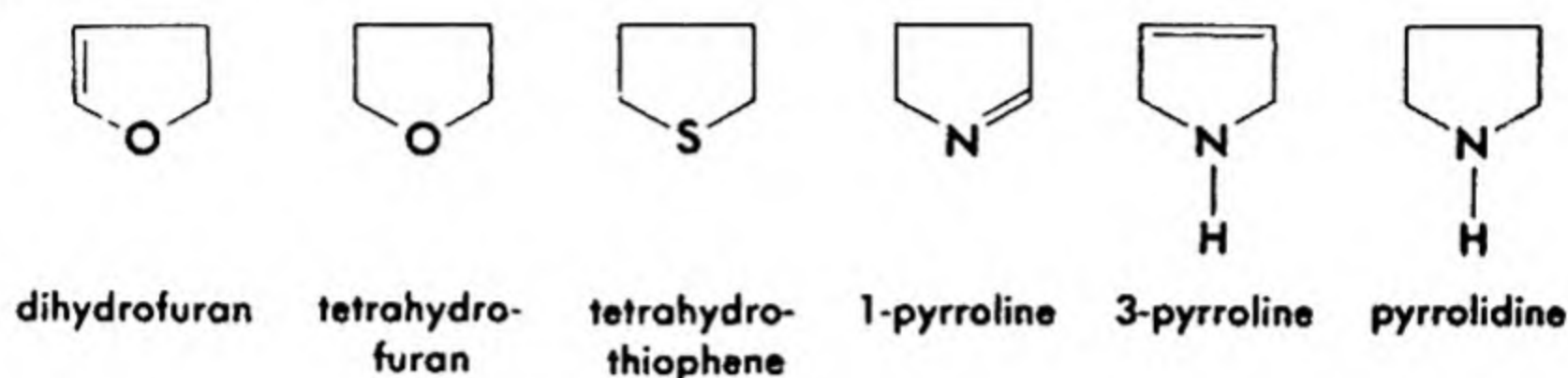
Since an electron pair is thus removed from the control of the hetero atom and placed in the overall pi orbital system, the hetero atom acquires a partial positive charge, the balance of the ring a partial negative charge. The intermediate sigma complexes (see below) involved in electrophilic substitution have charge distributions energetically little different from those of the corresponding substrate molecules, so that lower free energies of activation result than that with benzene. Thus, electrophilic substitution occurs much more readily in such heterocycles than in analogous carbocycles. Since charge delocalization in the α complex is better than that in the β complex, the transition state leading to the α complex has the lower energy, and α -substitution prevails.



However, the hetero atom may be a sensitive point in the ring; strong Brønsted acids must be avoided in substitutions in furan lest the ring be opened. Thus, special reagents must be used for substitutions, such as nitric acid and acetic anhydride instead of nitric acid and sulfuric acid, or pyridine-sulfur trioxide complex instead of fuming sulfuric acid.

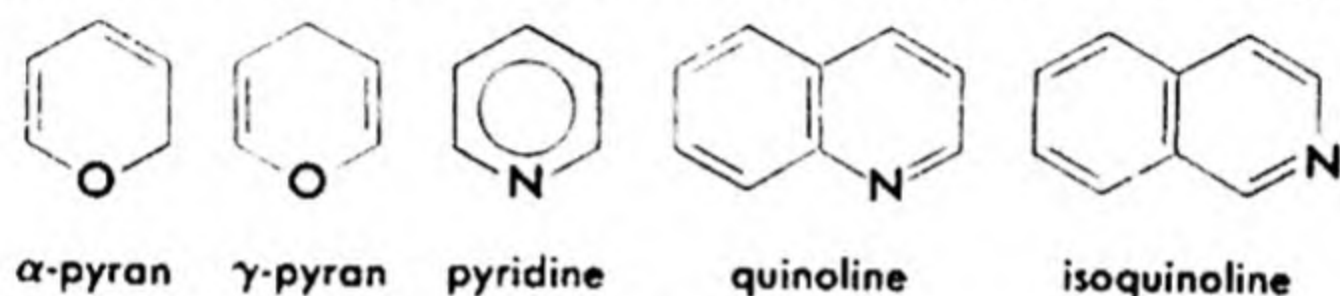
The ease of substitution in several aromatic systems is pyrrole > furan > thiophene > benzene. Thus pyrrole reacts with even dilute solutions of bromine to give tetrabromopyrrole, while furan may be brominated in a controlled fashion with bromine and without a catalyst, although in poor yields (side reactions occur). The bromination of benzene requires Lewis acid catalysis (§16-3A), while thiophene brominates in either or both α positions without such a catalyst.

Partial or complete saturation of rings removes the possibility of aromatic electron delocalization. Thus, dihydrofuran, tetrahydrofuran, tetrahydrothiophene, pyrrolines, and pyrrolidine resemble in chemical properties the respective open-chain ethers, sulfides, and amines of equivalent saturation.



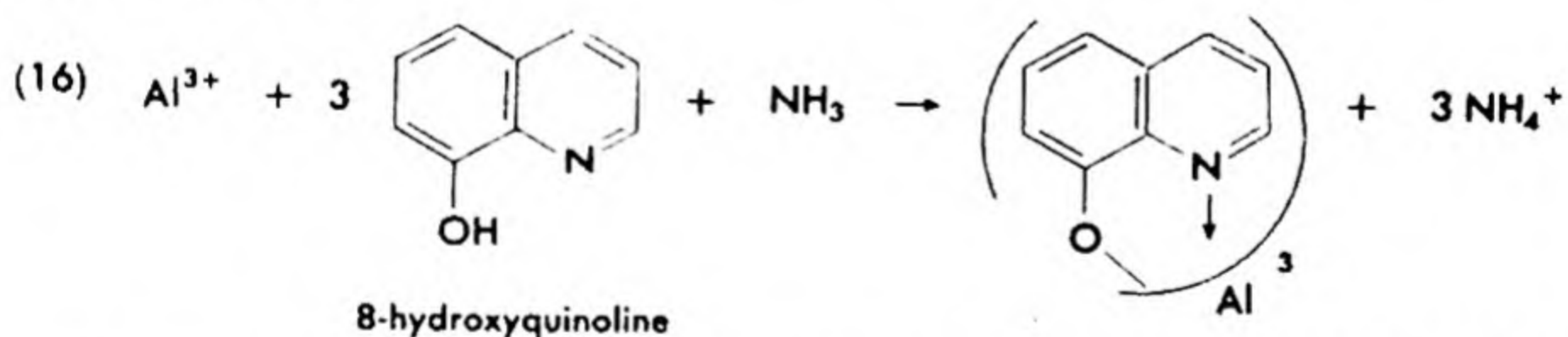
G. Six-Membered Heterocyclic Rings

Typical six-membered ring systems are the α and γ pyrans, pyridine and the benzopyridines, quinoline and isoquinoline. Pyridine is a commercially important solvent and raw material (as in the preparation of cationic surfactants, §40-3B). Pyridine, quinoline, and isoquinoline form



the basic systems for a number of naturally occurring and synthetic drugs (Table 42-4).

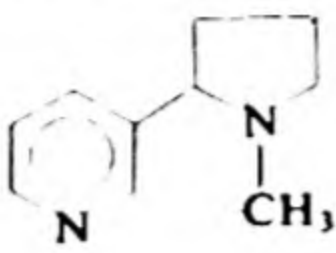
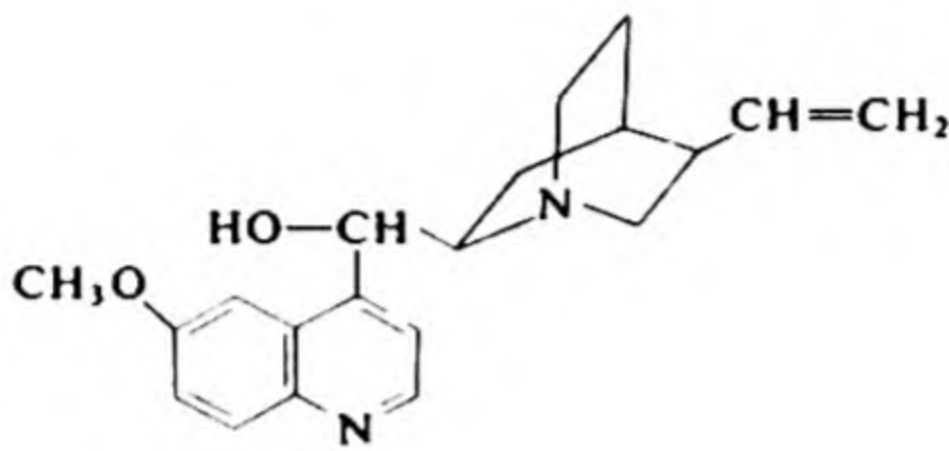
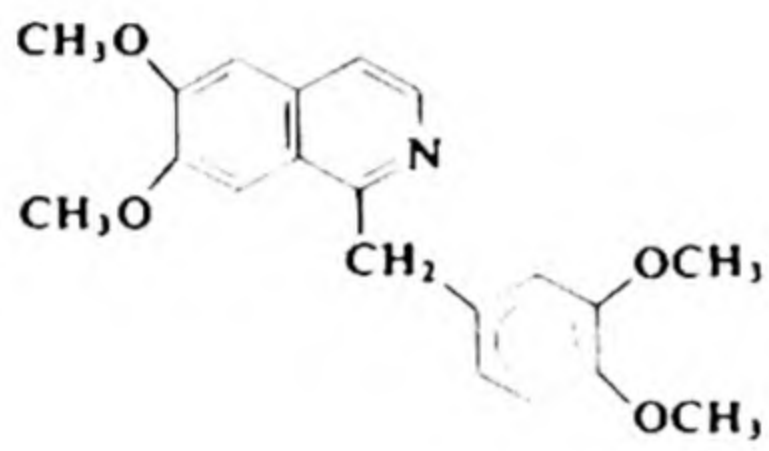
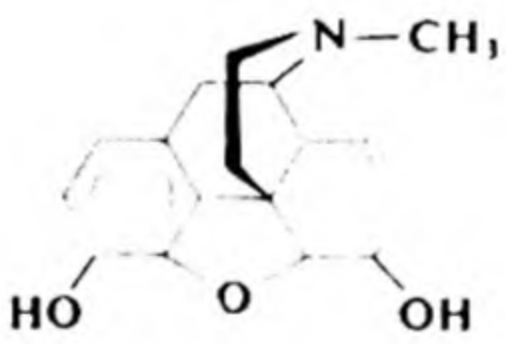
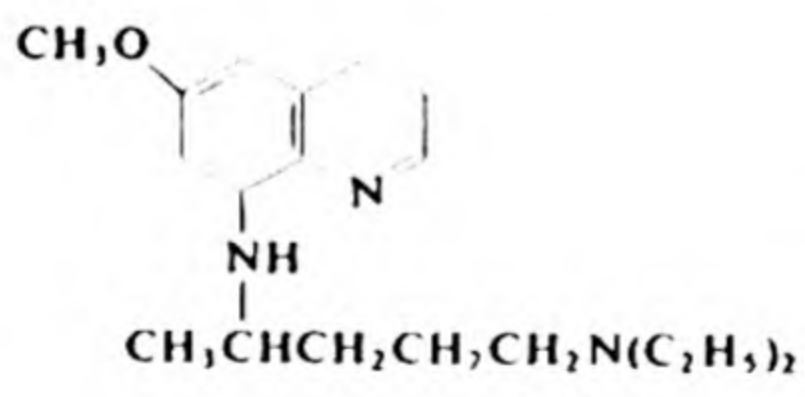
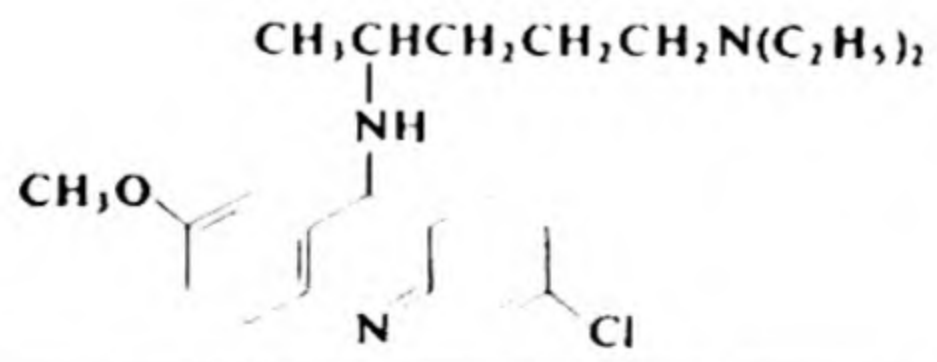
8-Hydroxyquinoline (oxine) is a quantitative precipitant for a number of metal ions and is used most extensively for aluminum (eq. 16) and magnesium. The oxinate is a neutral *chelate* (Gk., *chela*, crab claw) insoluble in water.

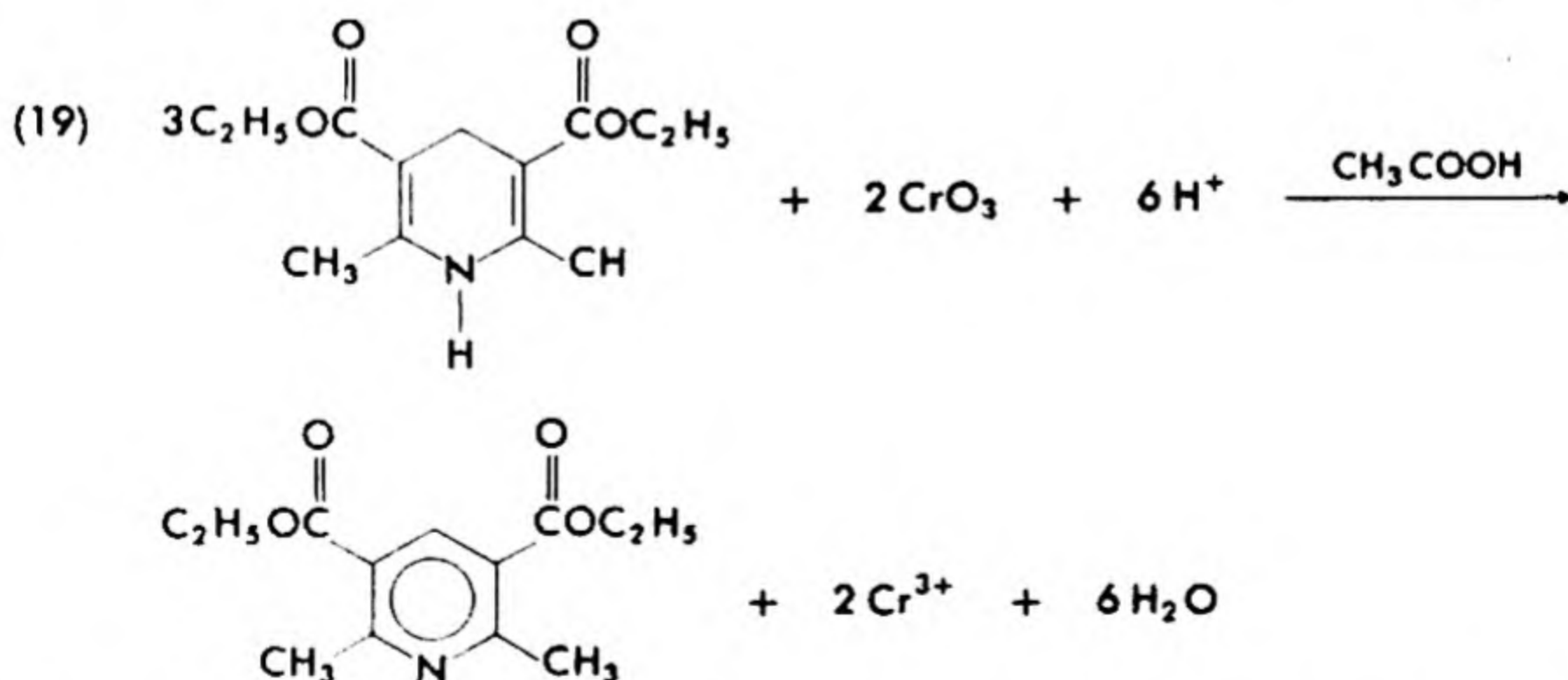
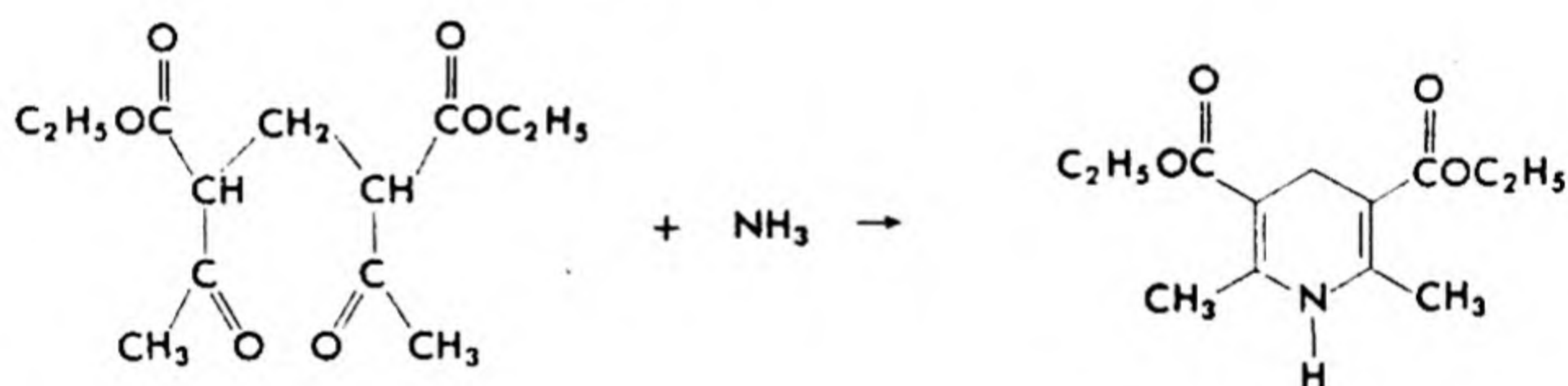
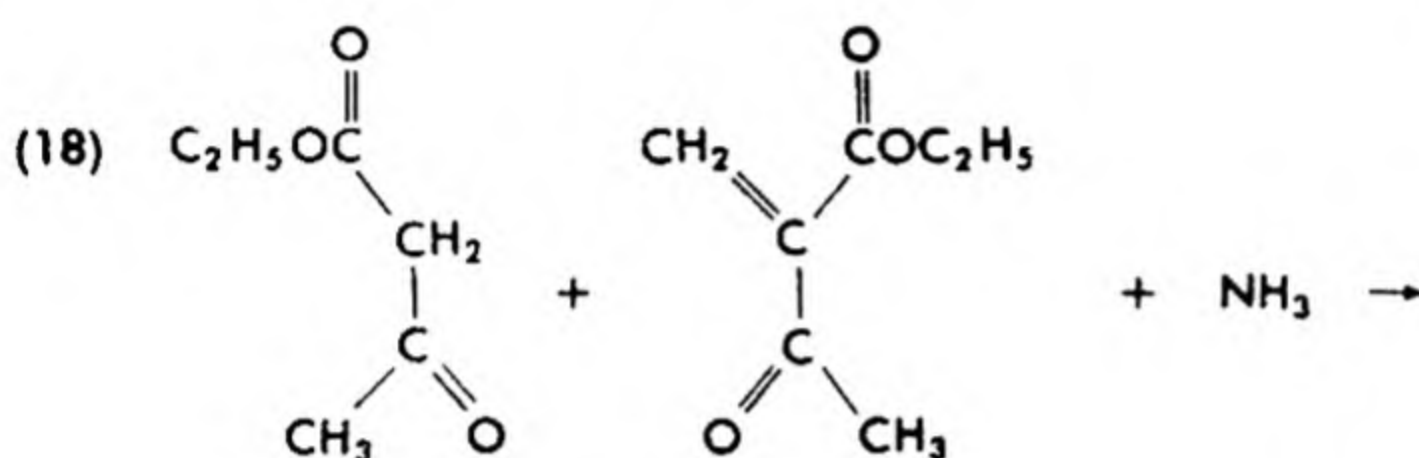
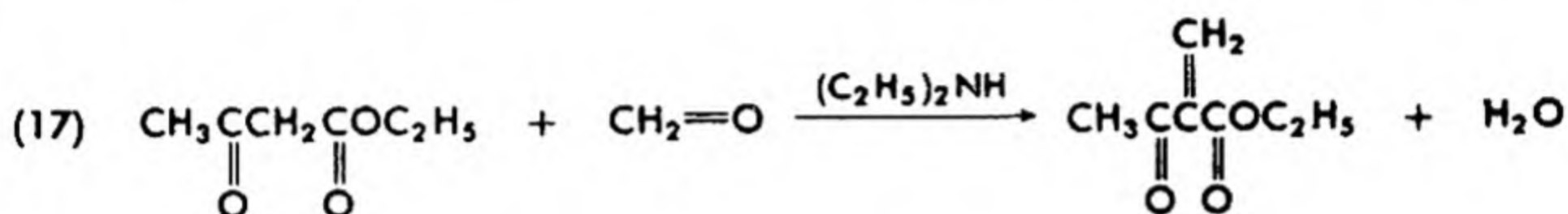
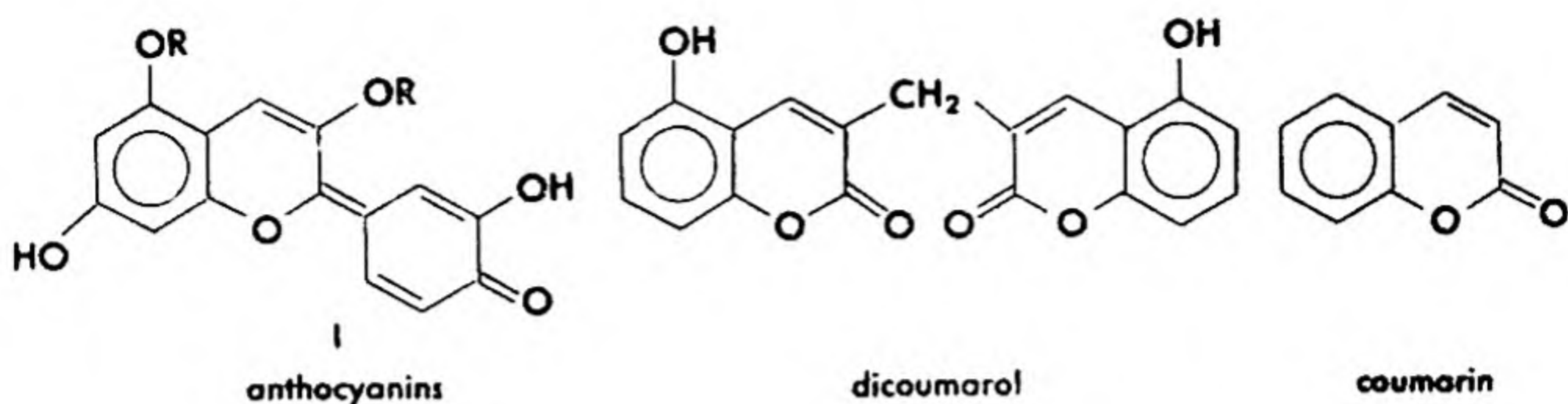


The simple pyrans have not been found or prepared. Their derivatives, however, figure largely in naturally occurring materials. The anthocyanins are flower pigments with structures such as I, in which R may be various carbohydrate units. Dicoumarol, an anticoagulant responsible for sweet clover disease of livestock, and coumarin, a flavoring agent resembling vanilla are naturally produced unsaturated δ -lactones (α -pyrones) (see p. 798).

(1) *Syntheses of Six-Membered Heterocyclic Rings.* Of the many methods of preparing pyridine rings, the Hantzsch synthesis (eqs. 17-19) is a typical example.

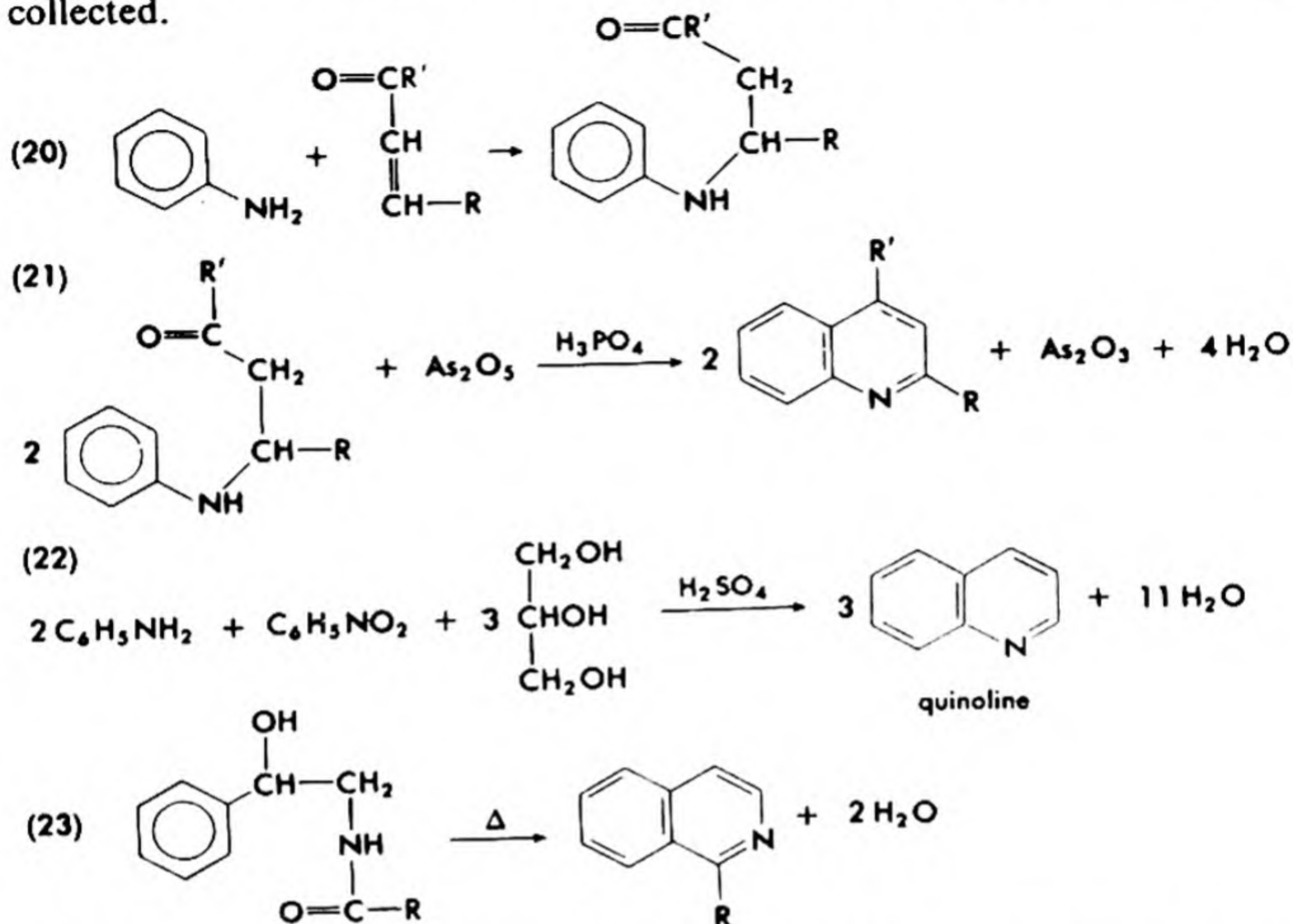
TABLE 42-4. Some Representative Drugs

Name	Structure	Comments
Nicotine		Principal alkaloid in tobacco; used as insecticide; also highly toxic to mammals
Quinine		Antimalarial from cinchona bark
Papaverine		Antispasmodic; from opium poppy
Morphine		Pain killer; from opium poppy; codeine is the methyl ether at phenolic O; heroin is the diacetate ester
Plasmochin (Pamaquin)		Synthetic antimalarial
Atabrin (Quinacrine)		Synthetic antimalarial

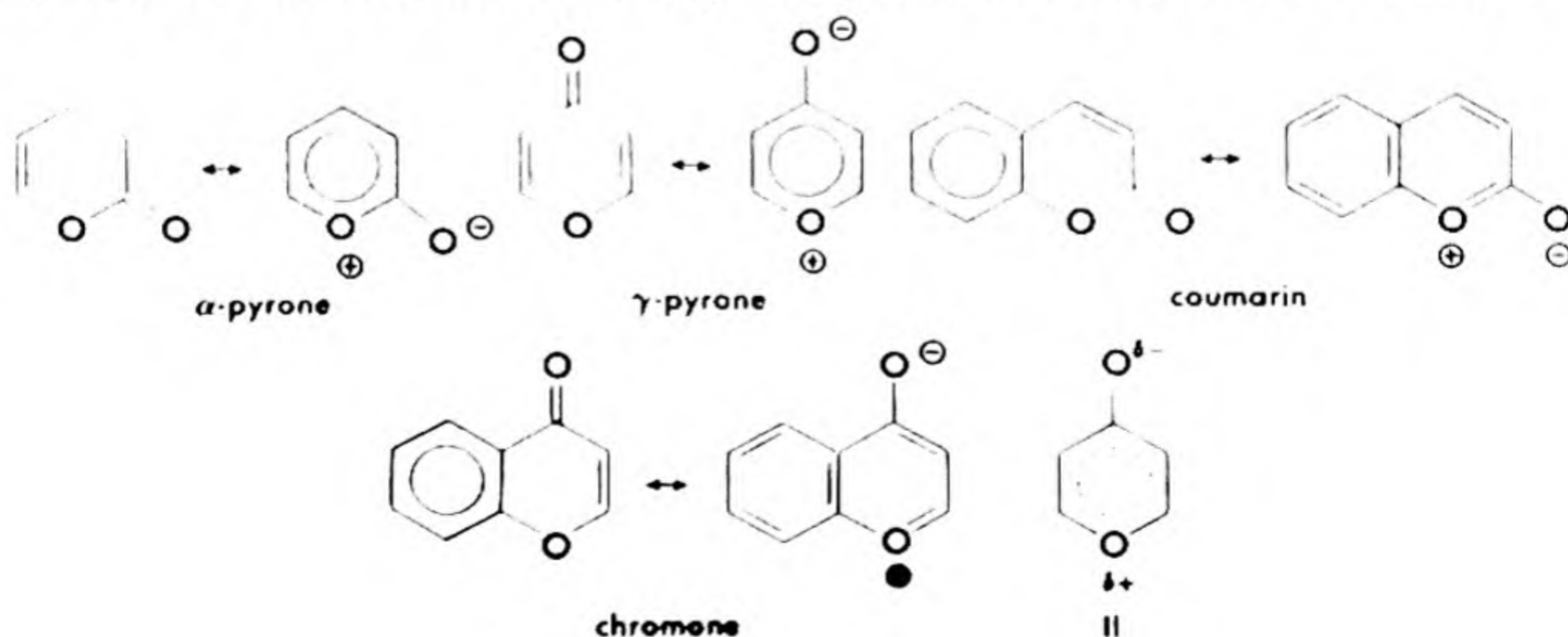


Syntheses of condensed heterocycles may involve condensation at active positions in an aromatic ring. Such are the *Skraup syntheses* of quinolines (eqs. 20-22) and the *Bischler-Napieralski synthesis* of isoquinolines (eq. 23). Note that eq. (21) combines a ring closure, a dehydration, and an oxidation. The reaction represented by eq. (22) has sometimes colloquially been called a "shotgun reaction"; it represents a type developed

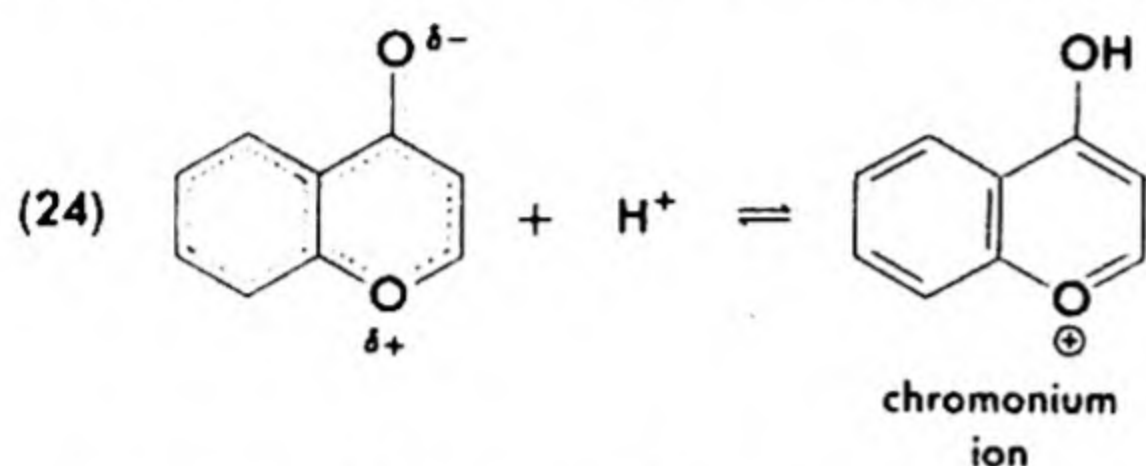
by early chemists in which everything was thrown together at once, heated to "shoot the works," and some of the desired product (hopefully) collected.



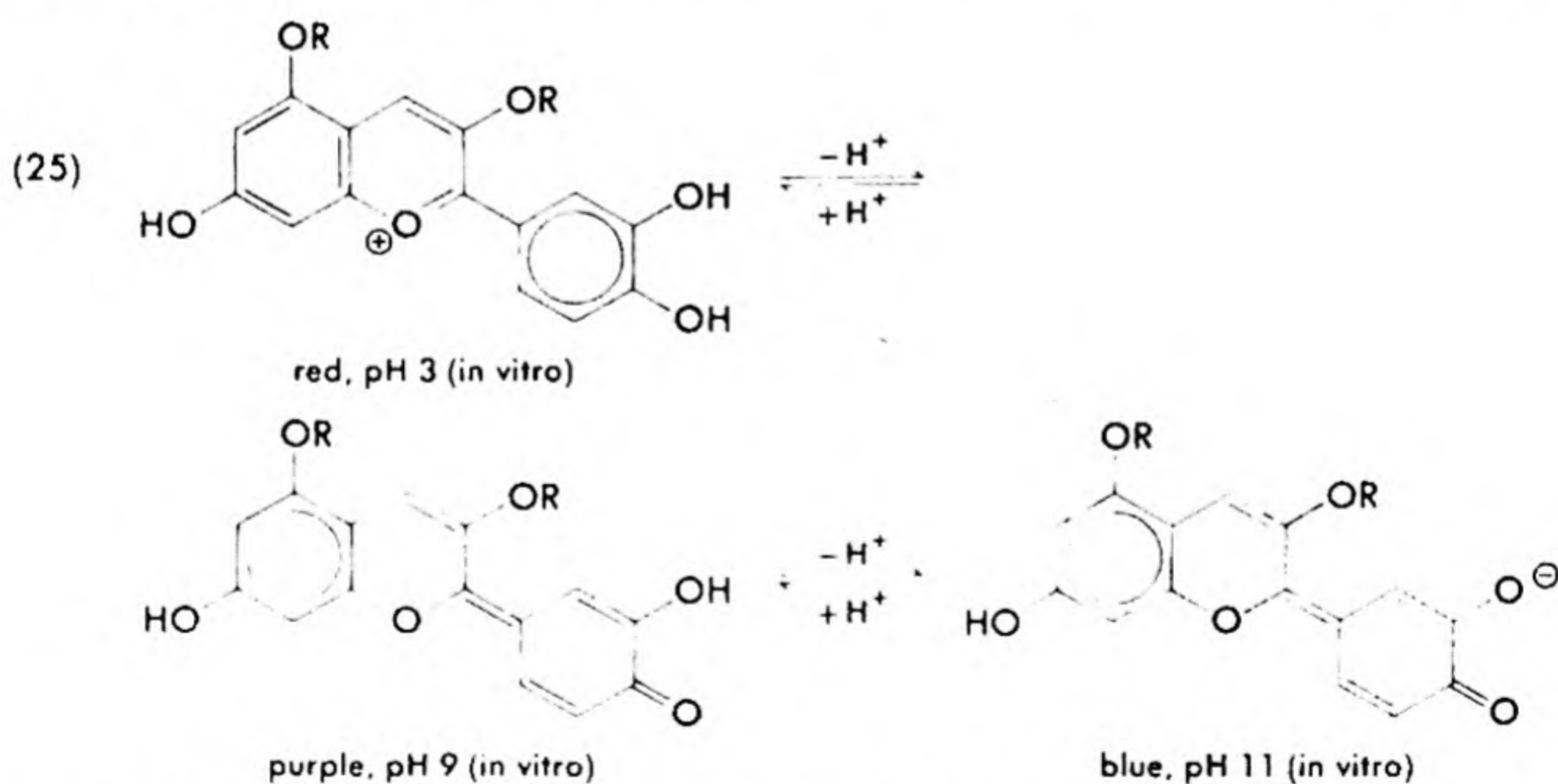
(2) *Chemical Properties.* Again, aromatic character is evident in many important heterocycles with six-membered rings. This is not unexpected in pyridine and its derivatives, since these are analogs of carbocyclic arenes in which N has replaced CH. In pyran derivatives, however, an aromatic system can be formed only when the oxygen atom acquires a formal positive charge. Thus, charge separation and consequent high polarity is evident in α - and γ -pyrones and their benzo derivatives, the coumarins and chromones. The participation of charged and uncharged



valence-bond structures with different apparent types of aromatic systems in the actual resonance hybrid (II for γ -pyrones) makes these highly complex aromatic systems difficult to analyze by the usual empirical approaches and also difficult to analyze by quantum mechanical approximations. Absorption maxima are shifted toward longer wavelengths (§33-2C) with the result that some of the salts of these compounds show color. Thus, for example, the chromonium salts are highly colored.

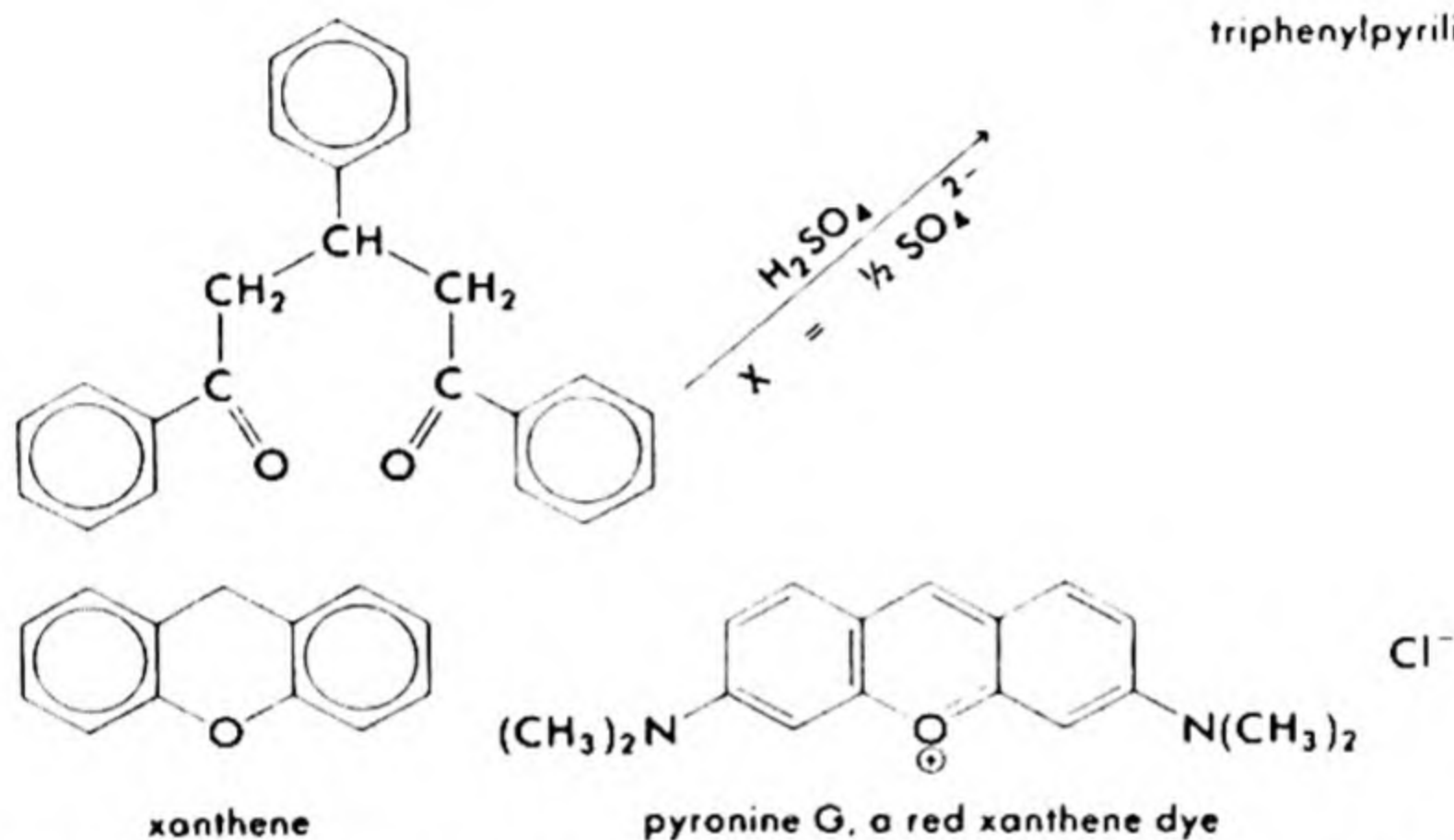
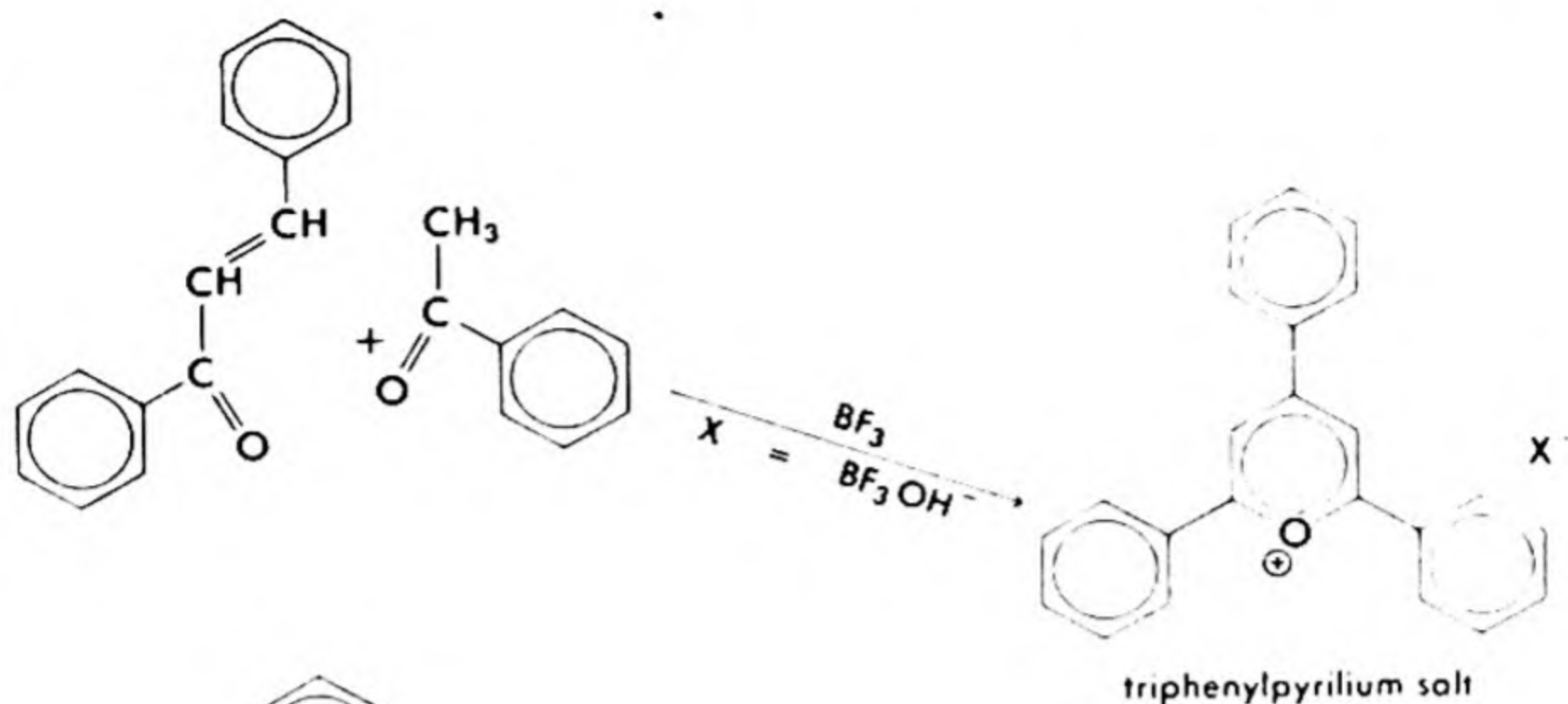


Reference to formula I shows that anthocyanins have an analogous, but still more complex system, the colors of which depend on pH; it is thus possible in special cases (e.g., the hydrangea) to produce flowers of different color by growing a plant in soil of different pH. More usually, the pH of the plant is internally regulated, but differs from one variety to another, so that a range of colors is possible by utilization of a single pigment. Factors other than pH also affect the system. Plant pH varies from 6.8 to 7.1, rather than 3 to 11, (outline 25). In this outline R represents H or a sugar unit.

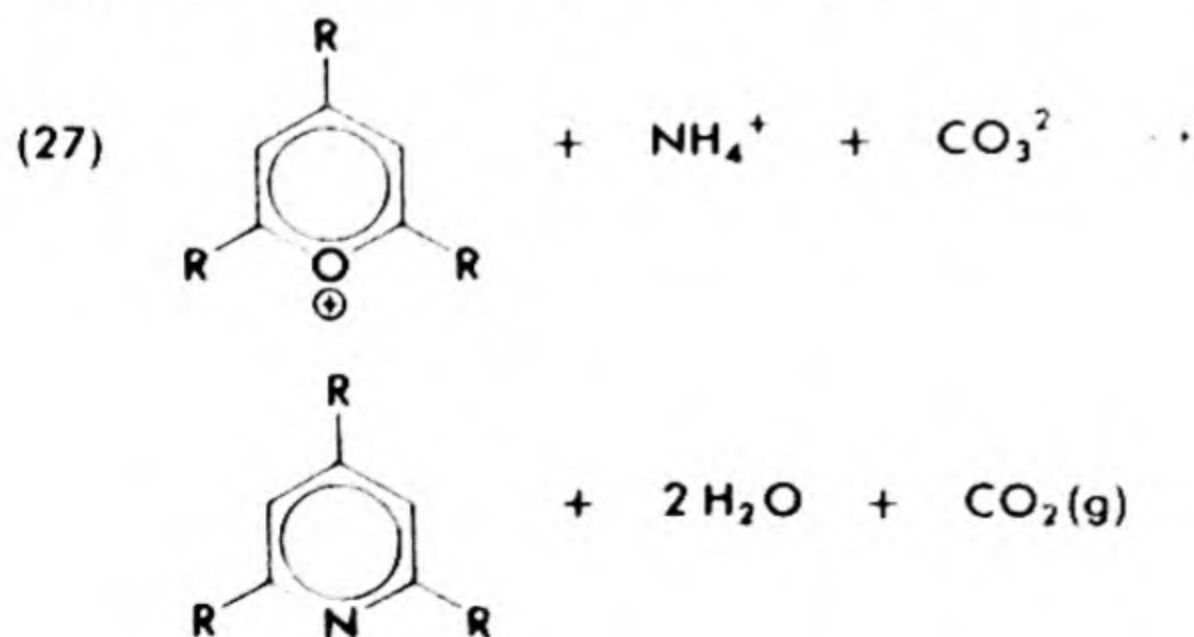


Pyrylium salts are aromatic systems which are derived from pyrans. The red form of anthocyanins (outline 25) is so classified, as are the simpler triphenylpyrylium salts formed from various ketones under the influence of strong acids (outline 26). Related compounds are dyes of commercial importance, called xanthenes from the parent system.

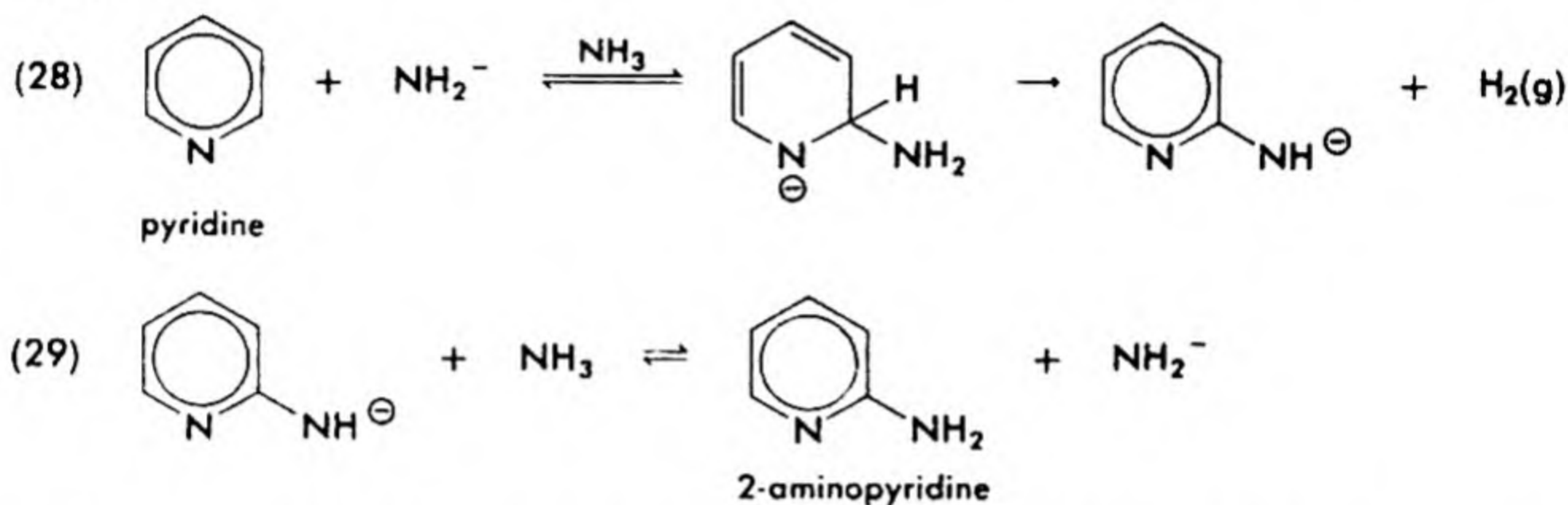
(26)



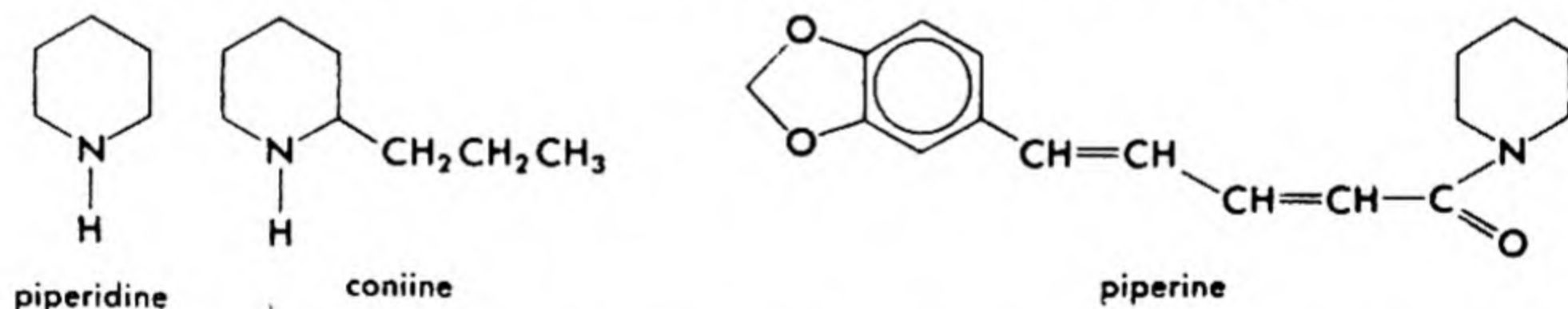
Note that aromaticity does not decrease the basicity of pyridine, since the unshared electron pair on the nitrogen atom is not involved in the aromatic orbitals. However, the differences in aromaticity of the Brønsted conjugate pairs in pyrone and pyrilium systems have strong influences on the acid-base equilibria of these compounds, as well as their ring-opening reactions. In general, pyrans, pyrones, and pyrilium salts are stable to acids, but readily cleaved by base. Thus, treatment of a pyrilium salt with ammonia or ammonium carbonate readily affords a pyridine by way of a ring opening and ring closure (eq. 27).



The inductive effect of the nitrogen atom in a pyridine increases the positive character of the ring, an influence detrimental to the stability of an electrophilic sigma complex, but favorable to the stability of a nucleophilic sigma complex. Thus, pyridines undergo electrophilic aromatic substitution much less readily than analogous carbocyclic arenes, but are readily substituted by strong nucleophiles, such as sodamide (eq. 28 and 29). Nucleophilic substitution occurs preferentially, as shown, in the α -position (2-position), or if this is blocked, in the γ -position (4-position). Electrophilic substitution occurs preferentially, but with difficulty, in the β -position.



The partly or fully saturated derivatives of pyridine and the pyrans have no aromatic character and resemble open-chain amines and ethers of comparable saturation. The most important of these is piperidine. The



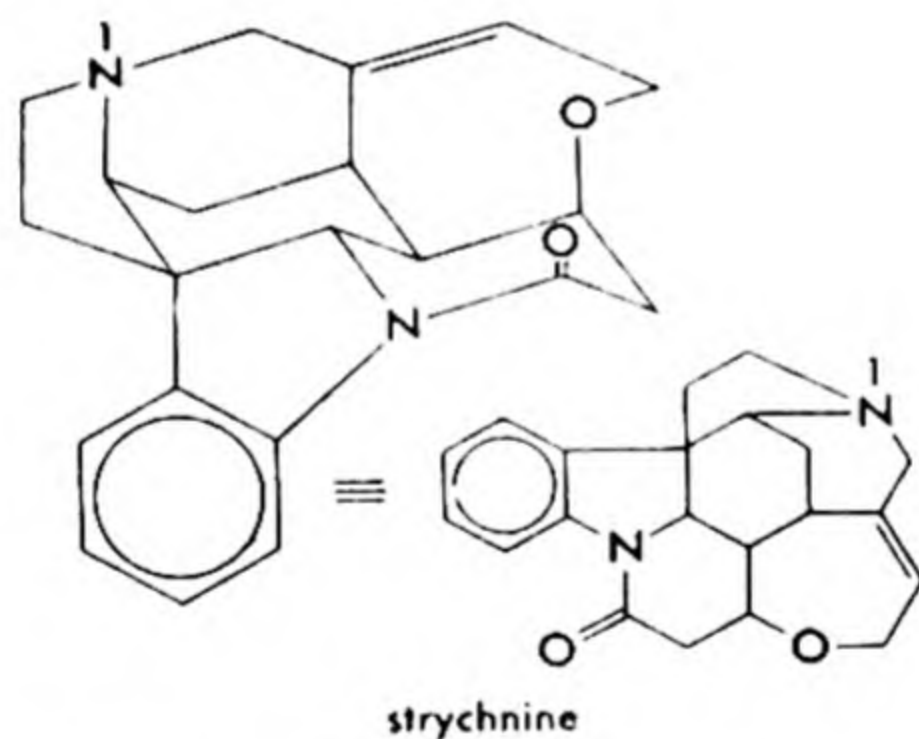
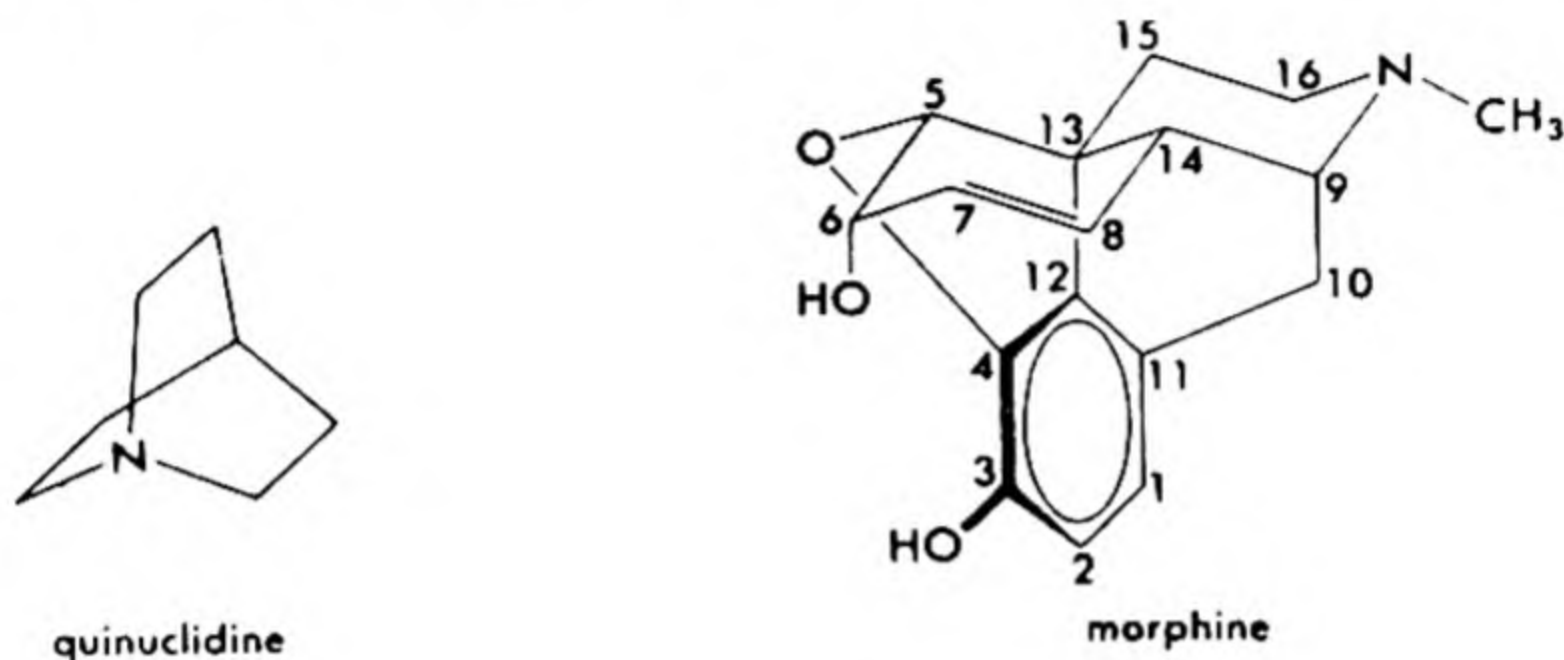
basicity of this compound and its derivatives is of interest in certain inorganic and analytical chemical uses such as complexing agents; the piperidine ring occurs in a number of naturally occurring alkaloids, such as coniine, which was the main constituent in the hemlock of Socrates, and piperine, an important constituent of black pepper.

H. Bridged Polycyclic Heterocycles

Heterocycles with bridged ring systems are very common among the *alkaloids*. These are plant products of bitter taste and generally basic character, with often very striking physiological effects in vertebrate animal systems. Most alkaloids seem to have little effect on their parent organisms; for example, tomato plants grafted to tobacco roots, and thus containing nicotine, have no apparent differences in growth characteristics from normal tomato plants. Similarly, tobacco plants grafted to tomato

roots, and thus lacking nicotine, apparently do not differ in growth characteristics from normal tobacco plants.

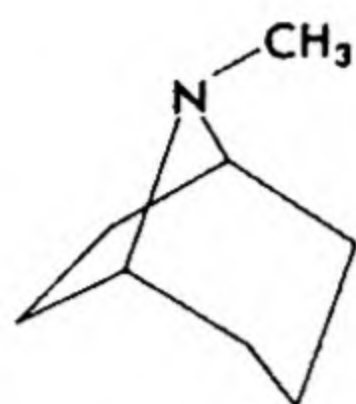
Some examples of alkaloids with bridged systems have been given. Quinine (Table 42-4) has the quinuclidine (1-azabicyclo[2.2.2]octane) ring. Morphine (Table 42-4) has a complex formula with the spatial arrangement shown below. From this, it can be seen that the phenyl group and carbon 10 form a bridge across positions 9 and 13 in the octahydroisoquinoline system, or carbon 14 forms the bridge across a benzoazacyclo-



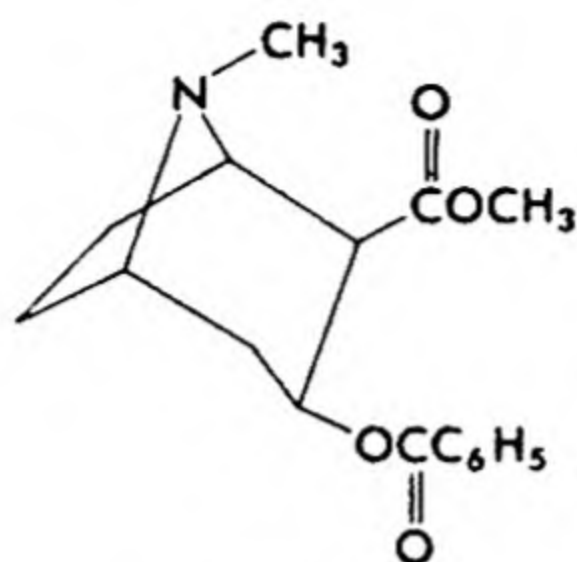
octane system, depending on the point of view. The most common viewpoint is that the nitrogen atom and carbons numbered 15 and 16 form a bridge across a hexahydrophenanthrene system, carbons 1-14. (This points up the difficulty of deciding upon a parent system for systematic nomenclature in such complex compounds.)

Another complex polycyclic bridge alkaloid is strychnine, a cardiac stimulant and rodenticide. The nitrogen atom numbered 1 is the center of a bridge across the cyclohexane ring in the center of the formula.

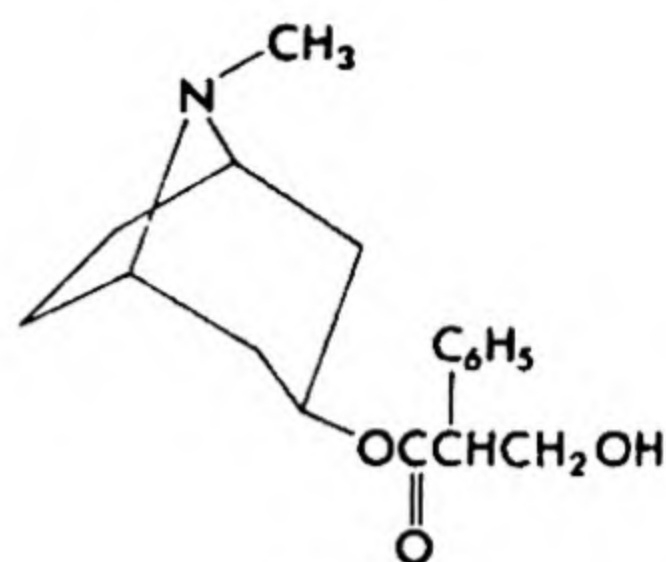
A large number of alkaloids of medicinal importance belong to the tropine group. These have the tropane (*N*-methyl-8-azabicyclo[3.2.1]octane) ring. Representatives of this class are cocaine, an alkaloid found in coca leaves and a narcotic used formerly as a local or topical anesthetic,



tropone



cocaine



atropine

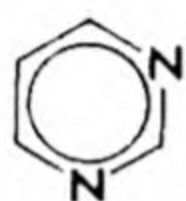
but abandoned because it causes addiction, and atropine, a belladonna alkaloid, very toxic, but used to relax smooth muscle tissue and as an antidote for phosphate nerve poisons (such as the insecticide parathion).

I. Heterocycles with More than One Hetero Atom

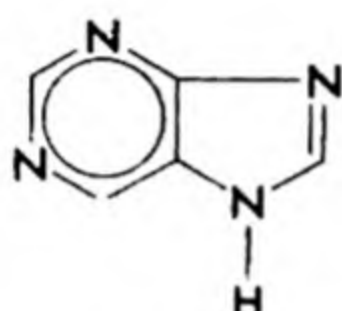
The fundamental systems of a number of important biochemical agents and drugs are imidazole, pyrimidine, and purine. These compounds, like



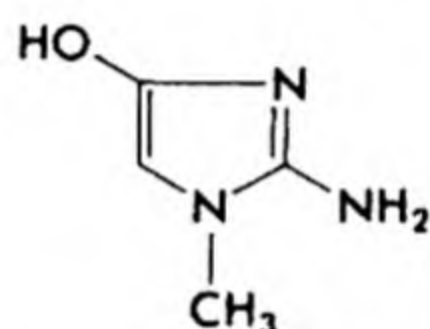
imidazole



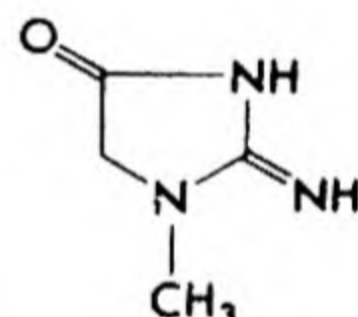
pyrimidine



purine



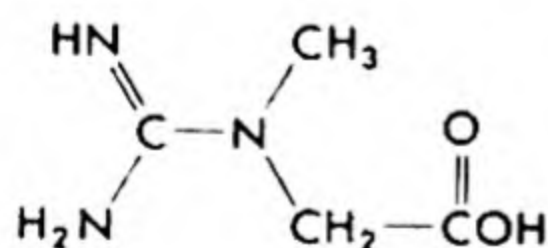
or



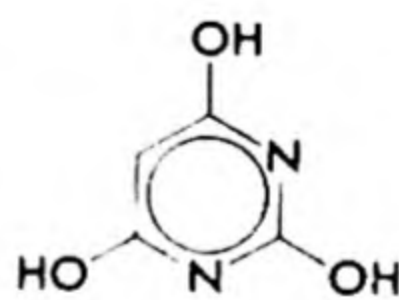
creatinine

the analogous pyrrole, pyridine, and indole, are aromatic, but some of their biochemically important substitution derivatives have groups which prevent some portion of the compound from forming a closed aromatic orbital system.

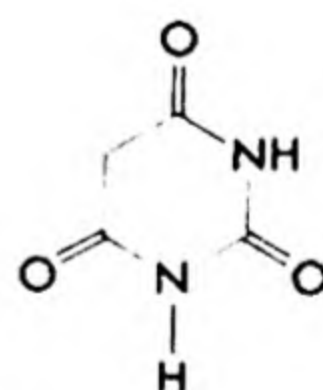
Creatinine is an imidazole derivative which is excreted as a biodegradation product of creatine, the *N*-phosphoryl derivative of which is a source of methyl groups in biosynthesis.



creatine



or

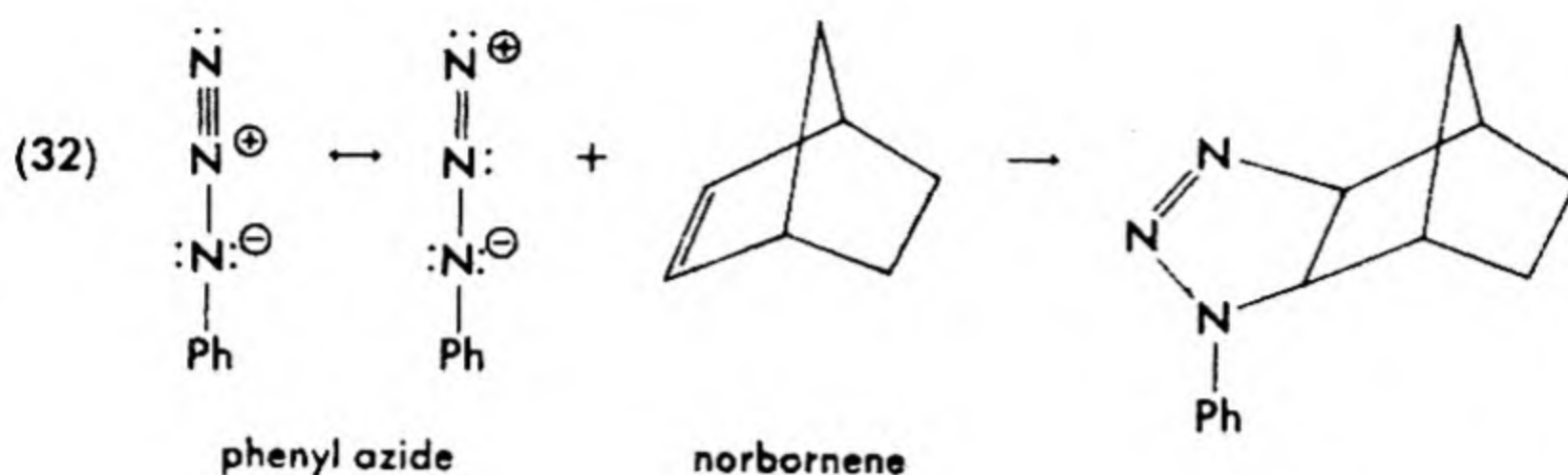


barbituric acid

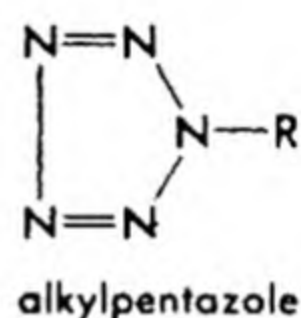
III A

III B

Participation of pyrimidine derivatives in important enzymes (§39-3B) and cell growth regulators (§43-3) leaves an opening for structurally related compounds to interrupt or divert biochemical processes. Such may be the mechanism of action of the hypnotics and soporifics called *barbitu-*

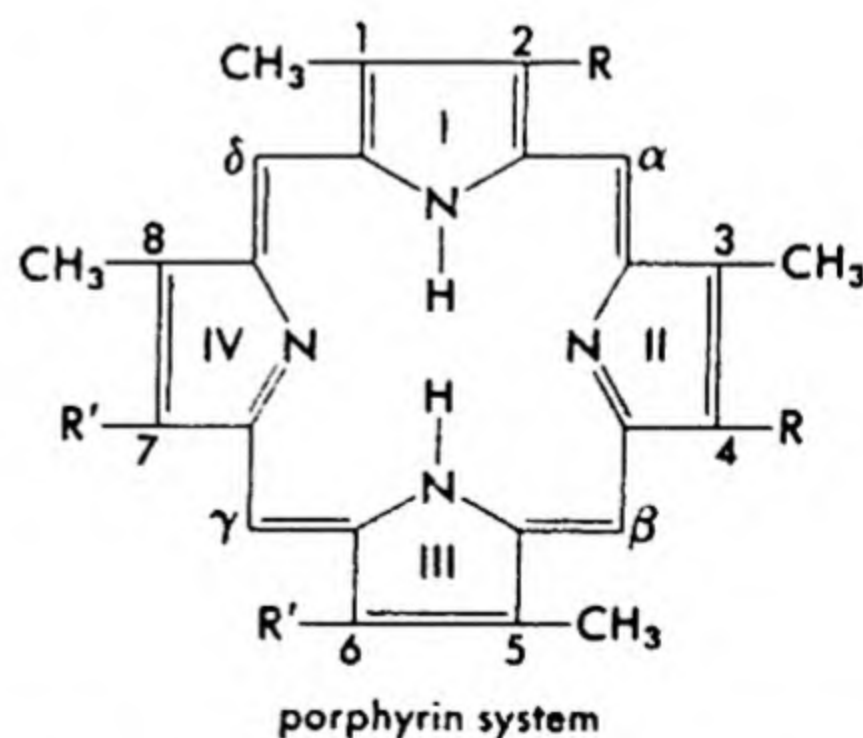
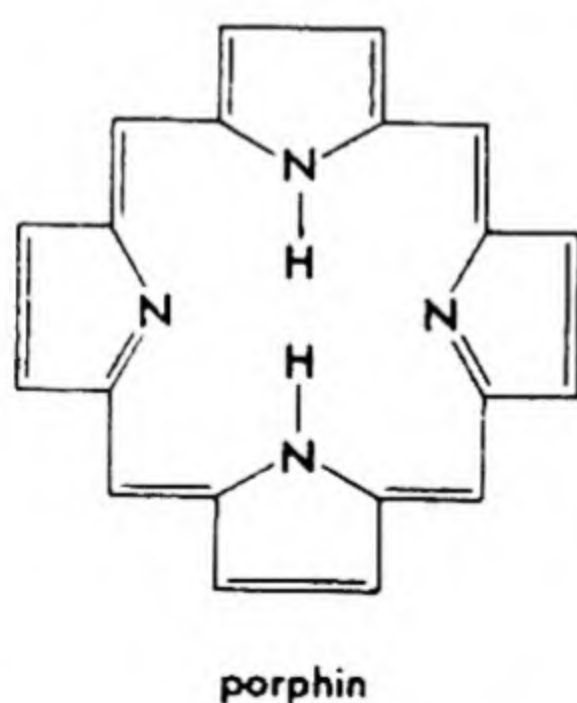


Other examples of such reactions already considered include the rearrangement of molozonides to ozonides (§27-1B) and the formation of pyrazolines from diazoalkanes and olefins (§24-3A). The reaction type is a general one for the preparation of heterocyclic compounds. Even substituted pentazoles have been prepared, although such compounds are highly unstable.

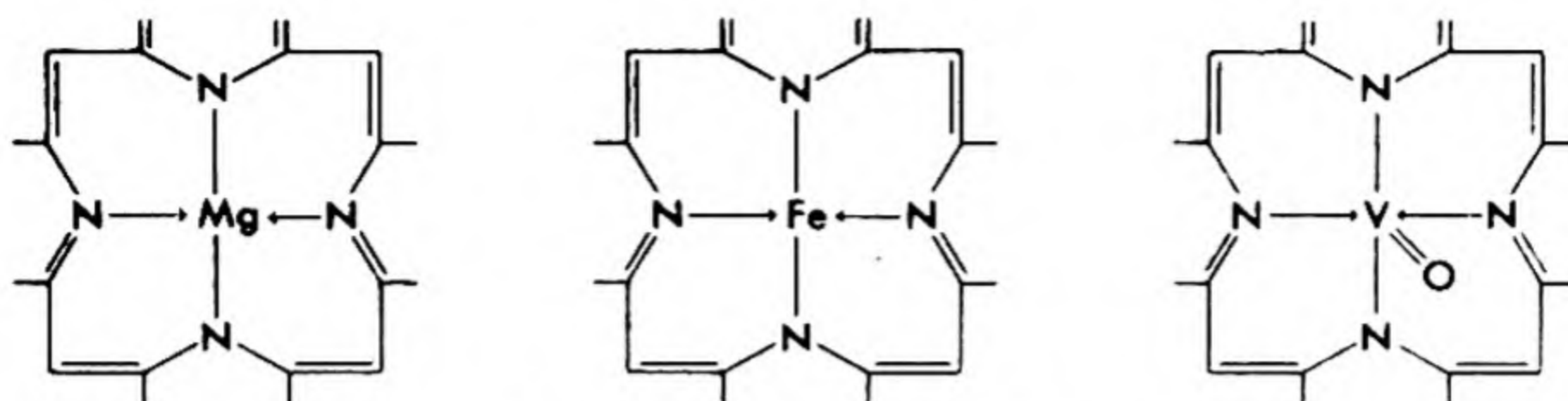


42-2 PORPHYRINS

Porphin is a compound having four pyrrole rings connected by methine groups at the 2-positions in a larger, resonating ring system. This ring system is the parent nucleus for a large number of physiologically important materials, such as hemoglobin, chlorophyll, and the cytochromes. Such materials are classed as *porphyrins*.



Most naturally occurring porphyrins conform to a structure such as that shown. The metal derivatives have magnesium, iron, copper, or other metallic ions in place of the two centrally located hydrogen atoms, and coordinated with the remaining two nitrogen atoms.



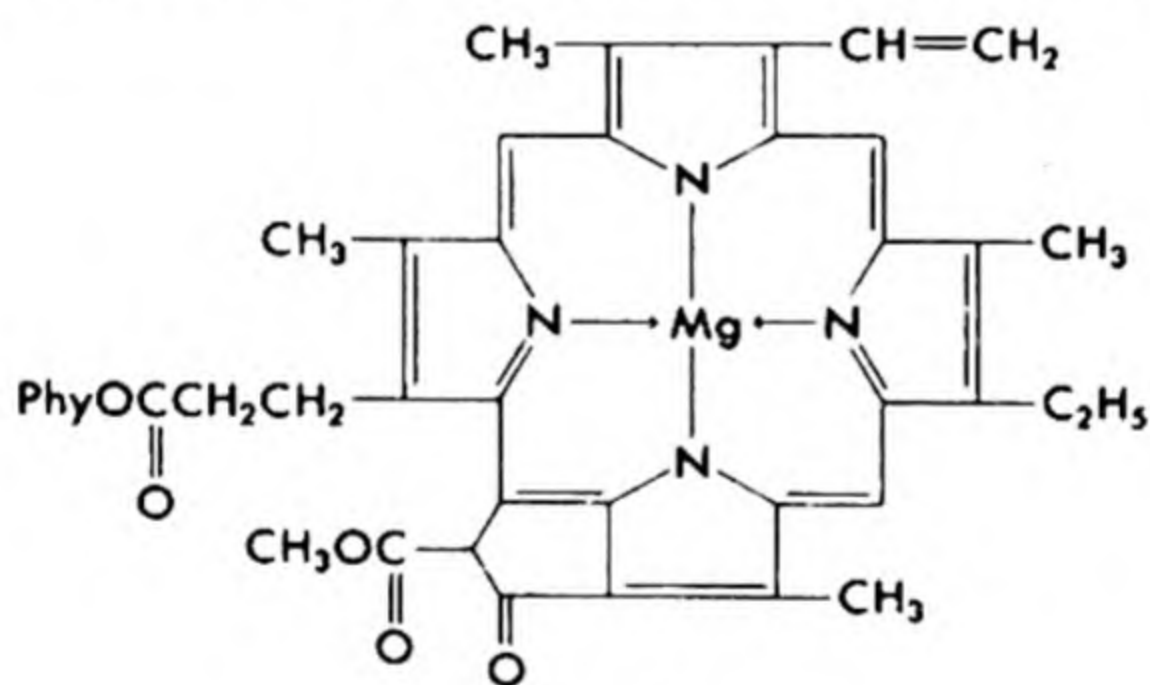
metal-porphyrin coordination systems

A. Occurrence and Biological Utilization of Porphyrins

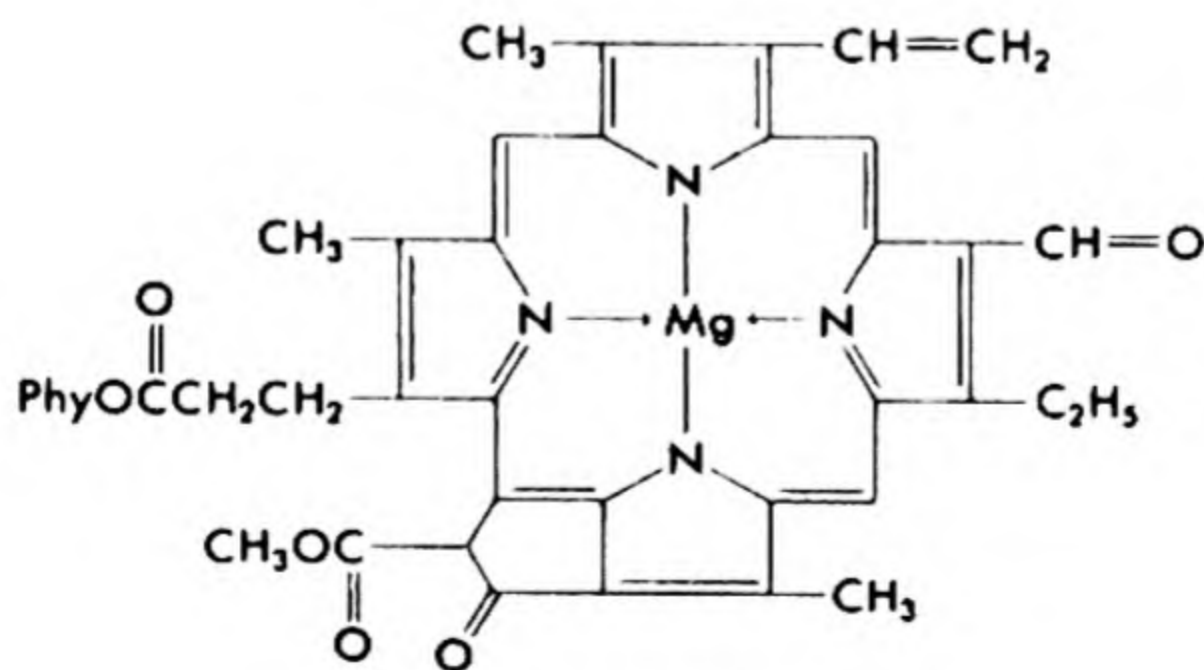
Hemoglobin is a chromoprotein which contains four heme units attached to a polypeptide chain. The heme units are ferroporphyrin units which carry oxygen in the blood.

Ferric cytochromes are oxidizing enzymes widely distributed among living organisms, in both the animal kingdom and the plant kingdom. These are chromoproteins with ferriporphyrin prosthetic groups (§39-3B).

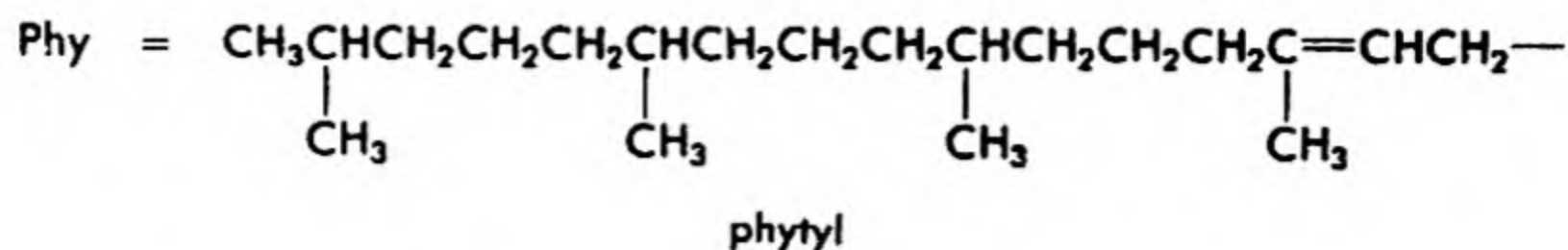
Chlorophylls are magnesioporphyrins, the roles of which are to absorb energy from red light radiation, and, thus activated, to reduce (through a sequence of reactions, §38-2B) water and carbon dioxide to glucose.



chlorophyll a



chlorophyll b



B. Structures of Porphyrins

The structures of porphyrins were considered to be elucidated only after a large number of degradations and syntheses, interlocking and cross-linked, had given the maximum probability of certainty of the structures of the numerous intermediates and final products. Much of the work was done by Hans Fischer, for which he received the Nobel Prize in 1930.

Degradation of a porphyrin with hydrogen iodide gives a number of pyrrole compounds, all containing a methyl group in the 3-position and either an ethyl group or a propionic acid group in the 4-position. Four variants of each of these types were obtained, the 2-methyl, 5-methyl, 2,5-dimethyl, and the compound without alpha methyl groups. These results suggested that the pyrrole rings were connected by one-carbon units at the alpha positions which formed a chain or ring of pyrrole units. Molecular weights of porphyrins agreed with compounds having four pyrrole units. The basic porphin ring structure was early considered a likely possibility.

To test the porphin ring theory, several known porphyrins and porphyrin-like compounds were synthesized. To make sure of the arrangement of groups on the 1,2,3,4,5,6,7,8-positions, the pyrroles were synthesized in several different ways, represented diagrammatically by Fig. 42-2. Each segment of the diagram represents a pyrrole ring.

To establish the porphin ring, three different tetramethyldipyrrolyl-methenes, represented by semicircles in Fig. 42-2A, were prepared. The first had bromine atoms on both terminal alpha positions, represented by notches. The second had bromomethyl groups on both terminal alpha positions, represented by burrs. The third had one alpha bromine atom and one bromomethyl-substituted alpha position. Treatment of a mixture of the first two with acid gave a tetrapyrrole compound identical with the product of treatment of the third alone with acid. The tetrapyrrole compound had the typical porphyrin absorption spectrum. Since the differences in alpha substituents gave no differences in product, the alpha methylene groups must have been involved in connecting the dipyrrolyl-methene units together. A large ring compound is the logical outcome, since the groups at each end should behave alike.

Proof of the ring structure depended on assembling a tetrapyrrole with at least three different sets of substituents, represented by 1, 2, and 3 in Fig. 42-2B and C. To get the same product by putting together the dif-

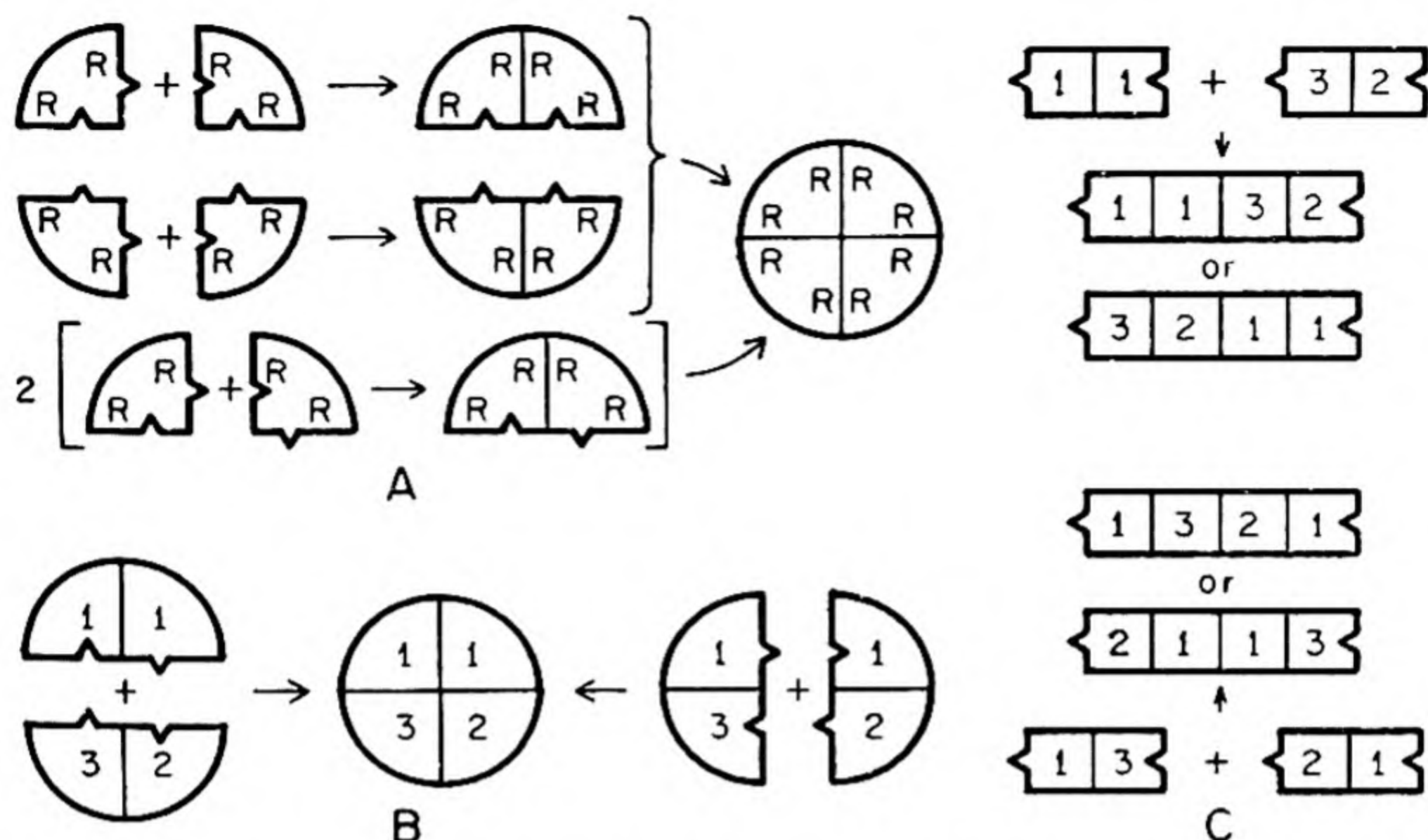
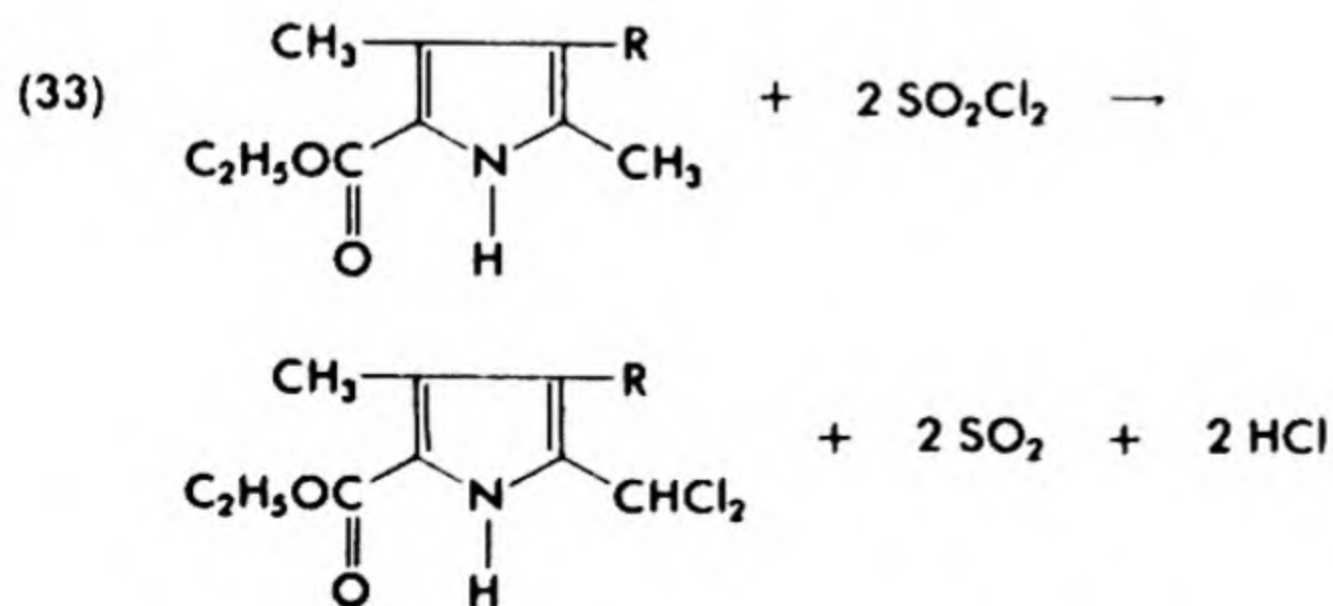
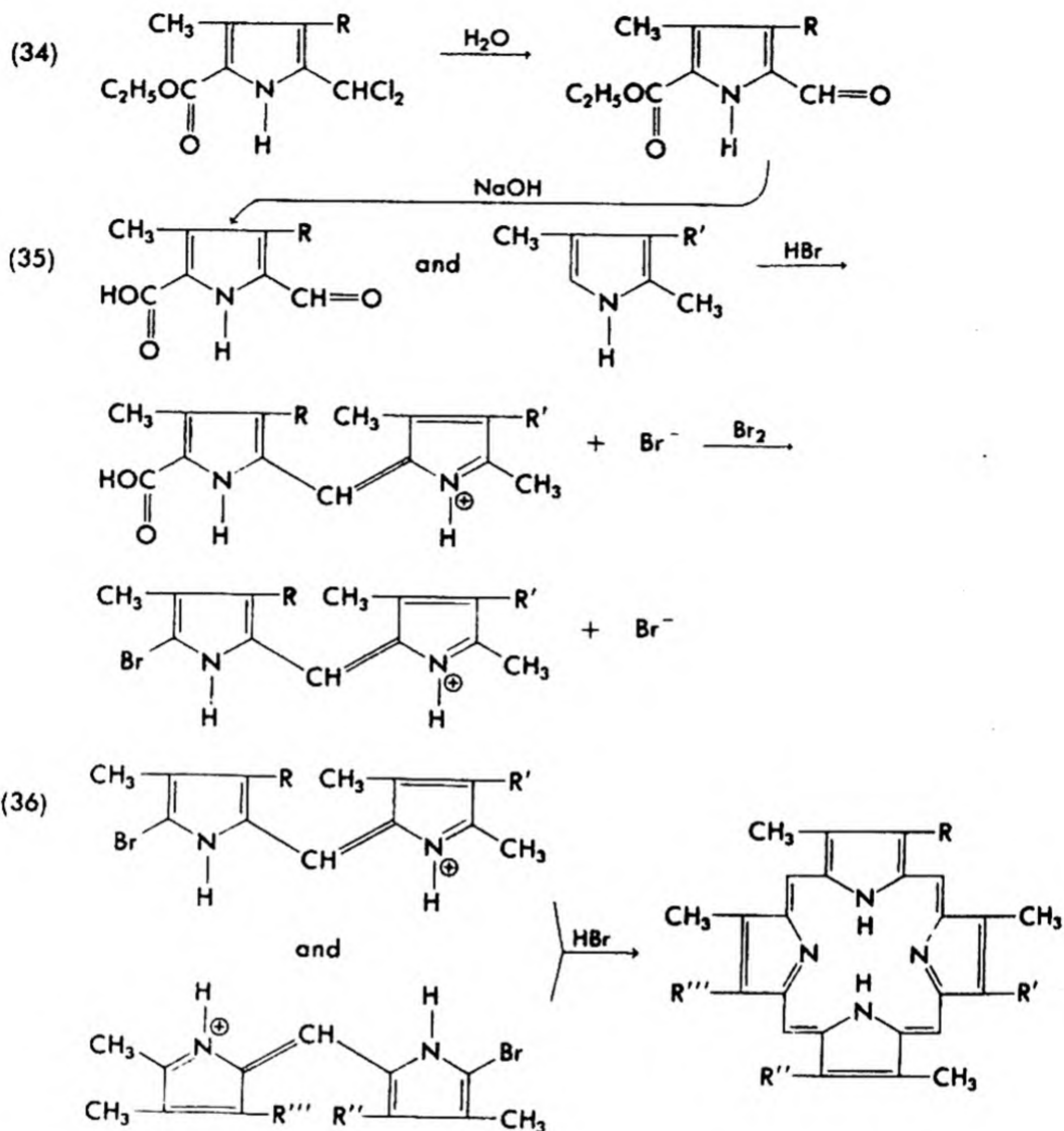


Fig. 42-2. Schematic Representation of Synthesis of Porphyrins from Pyrroles.

ferent sets of halves, 1-1 and 2-3, or 1-2 and 3-1, requires a cyclic structure (Fig. 42-2B) rather than linear structures (Fig. 42-2C).

The problem then resolved to the synthesis of pyrroles with different substituent groups in different positions such that the positions of substituents were unequivocal, and then piecing the parts together in such a way that the order of substituents about the porphyrin ring was unmistakable. The first part of the task was the more difficult. The positions of substituents were established beyond doubt by a series of degradations and concurring syntheses by different routes. Methods of synthesizing pyrroles have already been discussed. Means by which pyrroles were assembled into a porphyrin are indicated in equations and outlines (33-36).





42-3 PYRIMIDINES, PURINES, AND NUCLEIC ACIDS

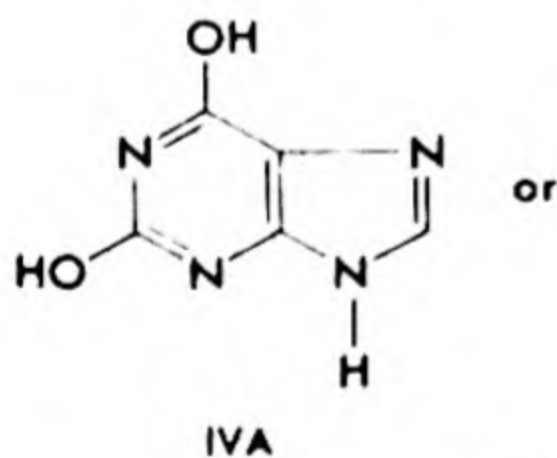
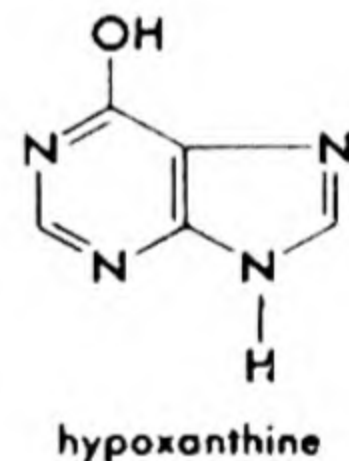
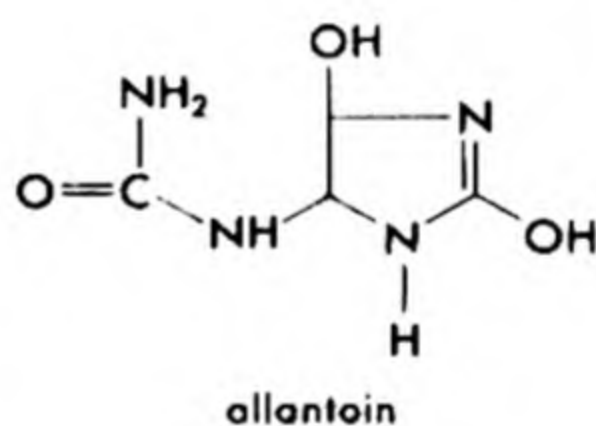
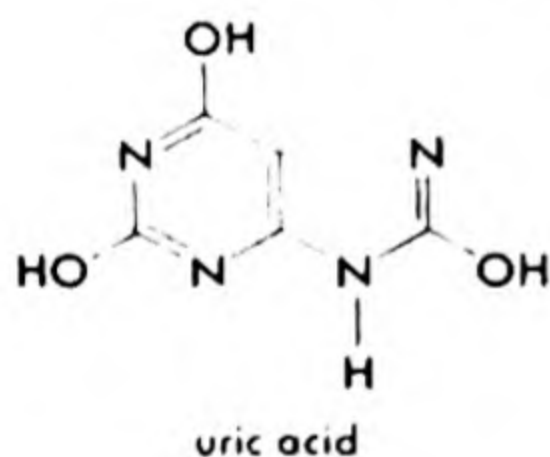
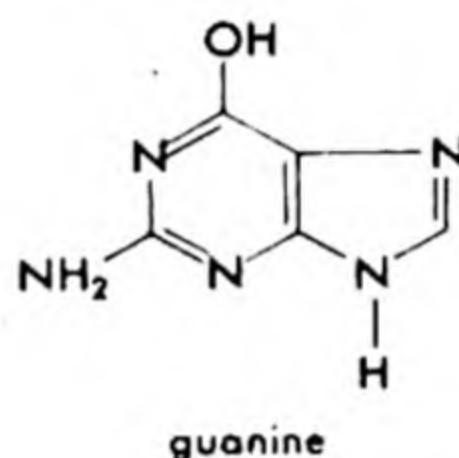
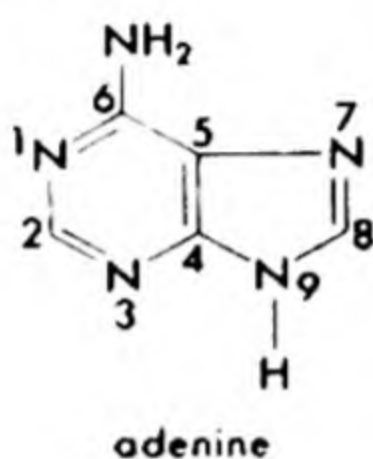
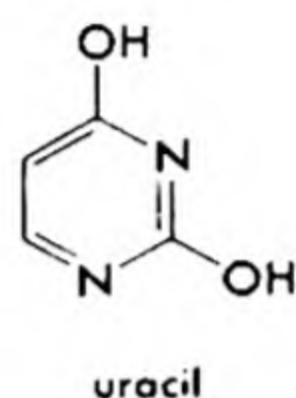
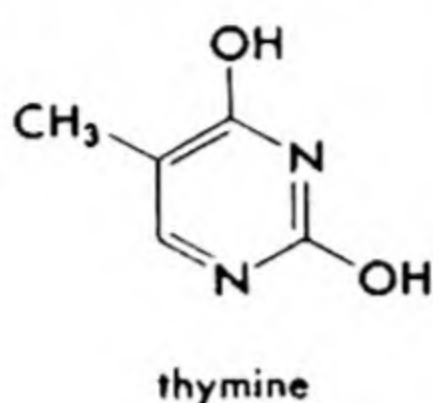
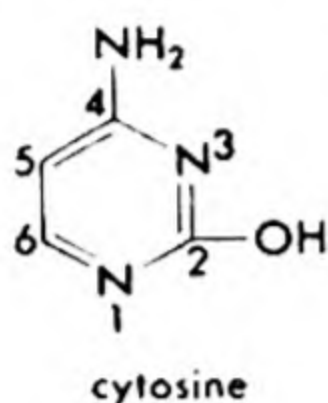
Nucleic acids are high molecular weight prosthetic groups of nucleoproteins, so called because they occur in cell nuclei. Genes, viruses, and bacteriophages are composed almost exclusively of nucleoproteins.

Nucleic acids are composed of pyrimidine and purine bases, pentoses, and phosphate groups. Their structures are very complex and have only recently begun to be elucidated. The pyrimidines and purines present in nucleic acids and their close metabolic relatives are the heterocycles under consideration in the section following.

A. Metabolic Pyrimidines and Purines

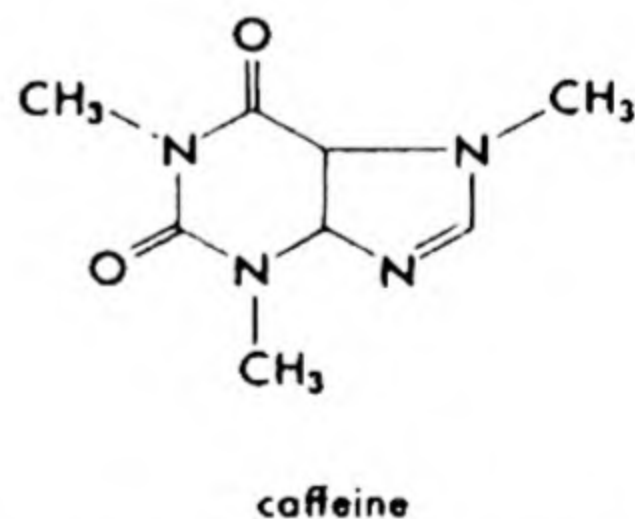
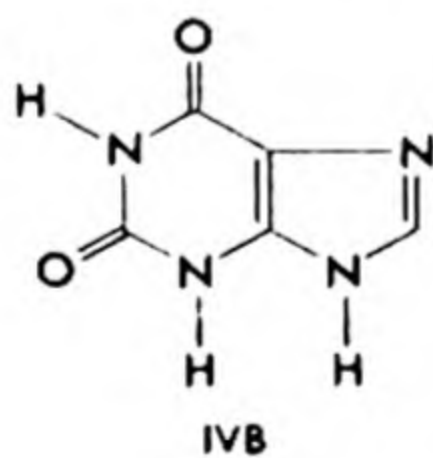
At least six of the several naturally occurring heterocyclic related bases are known to occur in nucleic acids. These are the four pyrimidines,

cytosine, 5-methylcytosine, thymine, and uracil, and two purines, adenine and guanine. Upon degradation of nucleic acids, the higher primates (including man), the Dalmatian coach hound, birds, and reptiles convert the bases into uric acid, below, which is excreted in the urine. Other mammals excrete the purines and pyrimidines in the form of allantoin. Two other purines found in body fluids are hypoxanthine and xanthine.



or

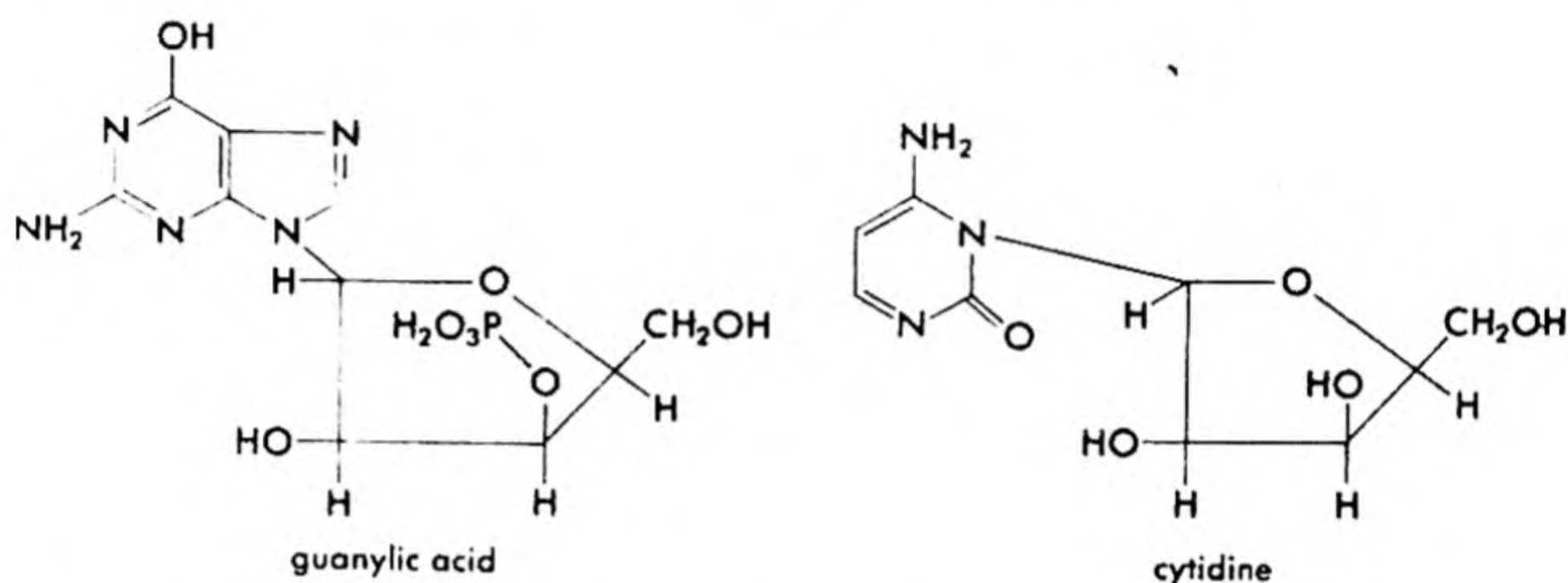
xanthine



Three xanthine derivatives are of interest because of their occurrence in plants used for beverages and confections, partly because of their stimulant action. These are caffeine, 1,3,7-trimethylxanthine (in coffee), theobromine, 3,7-dimethylxanthine (in tea), and theophylline, 1,3-dimethylxanthine (in chocolate and cocoa). These compounds are all related to the amide tautomeric structure (IVB) of xanthine, rather than the imidol structure (IVA).

B. Nucleotides and Nucleosides

Careful hydrolysis of nucleic acids gives compounds which must be a repeating structural unit in the polymers. These are called *nucleotides*, and consist of one purine or pyrimidine base, one pentose, and one phosphate unit each. Further hydrolysis with acid gives a pentose phosphate and the free base. Hydrolysis of the nucleotide with base gives a *nucleoside*, consisting of a base-pentose unit, and phosphate ion. Hence, the sugar must be between the base and the phosphate in the nucleotide. The sugars from known nucleic acids are ribose and 2-deoxyribose (2-deoxyribose). Thus, guanylic acid is a nucleotide, as is also adenylic acid (§39-2B). Cytidine and adenosine (§39-3B) are nucleosides.



Several nucleotides not derived from nucleic acids exist in living organisms. Some of the more important nucleotide coenzymes have already been mentioned (§39-3B).

C. Nucleic Acids

The importance of nucleic acids is their fundamental role in the most basic processes of life, cell reproduction, cell metabolism, and intercellular organization.

Deoxyribonucleic acids (DNA) hold the *genetic code*, that is, the key to the development and organization of cells. By *replication*, these acids duplicate themselves and make possible cell division. DNA occurs in twinned helices (inside back cover) in the cell nucleus. The alternate deoxyribose and phosphate units constitute the helical "stringers" of a staircase-like structure. The inner, "step" portion is made up of pairs of purine and pyrimidine bases (one of each), hydrogen bonded together in a specific orientation and in a specific pairing of bases (Fig. 42-3). Guanine pairs only with cytosine or 5-methylcytosine, and adenine only with thymine (in DNA) or uracil (in *ribonucleic acid*, RNA). Periodically, the twinned helix uncoils, in response to some cellular condition, to form two separate chains. Freshly made nucleotides then condense on the old

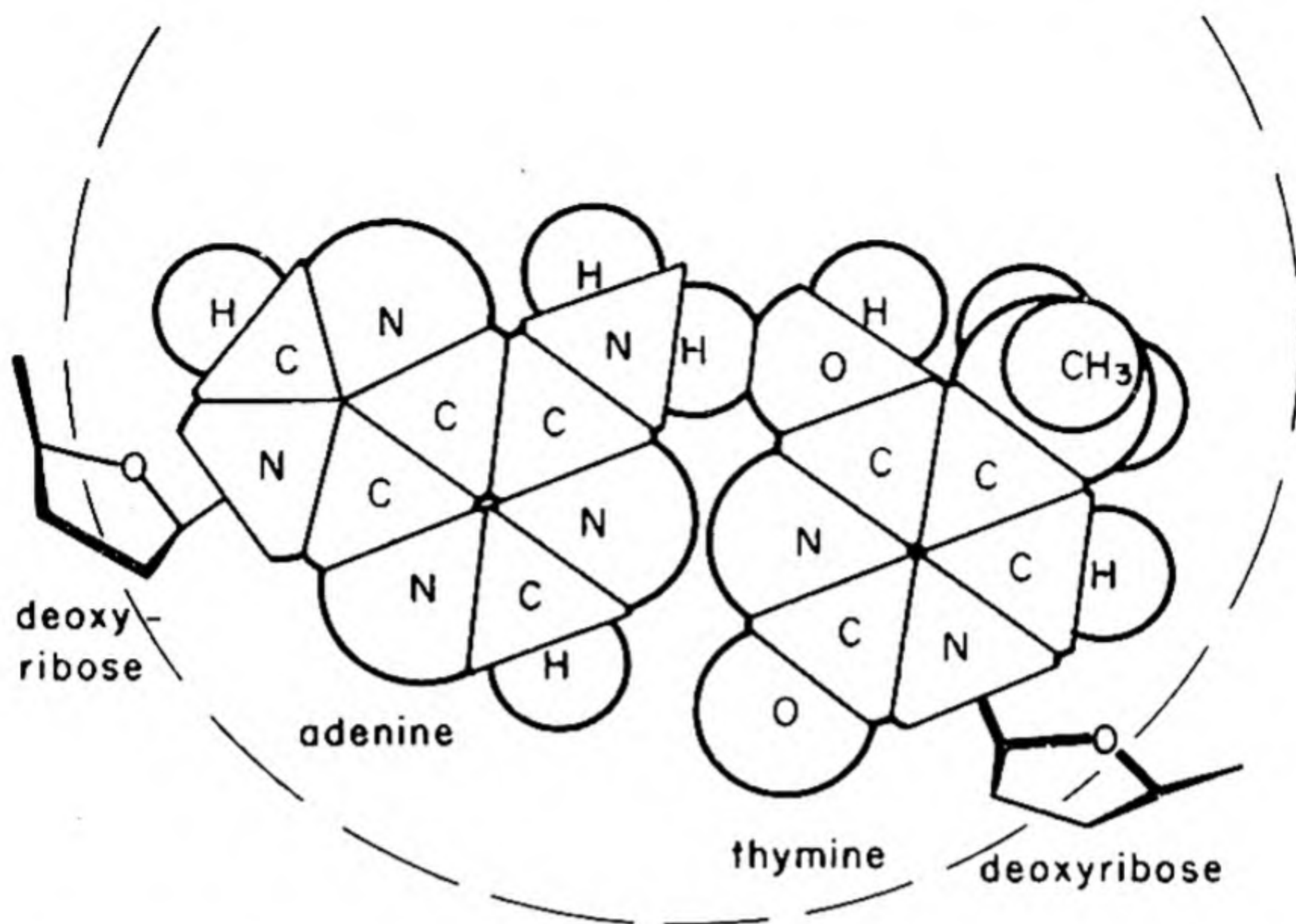


Fig. 42-3. A Purine-Pyrimidine Layer in a Nucleic Acid Spiral.

chains in such a manner as to preserve the pairing order. The result is two new helices identical to the original; this is replication.

DNA also regulates the formation of RNA, which functions in the cytoplasm. RNA carries the *growth code*, i.e., the key to the synthesis of proteins in the cell. The four different purine and pyrimidine bases can form 64 different 3-unit code units ("words") depending on combination and order of connection of the nucleotide units. Of these, at least twenty "words" correspond directly to specific amino acids. Thus, a RNA chain constitutes a direction to synthesize a protein with amino acid units in a specific order. More details of the process are available in Crick and Nirenberg, listed in the Supplementary Readings.

SUPPLEMENTARY READINGS

- Acheson, R. M., *An Introduction to the Chemistry of Heterocyclic Compounds*, Interscience, New York, 1960.
- Allen, F. W., "The Biochemistry of the Nucleic Acids, Purines and Pyrimidines," *Ann. Rev. Biochem.* **10**, 221 (1941).
- Badger, G. M., *The Chemistry of Heterocyclic Compounds*, Academic Press, New York, 1961.
- Corwin, A. H., "The Chemistry of the Porphyrins," in H. Gilman, *Organic Chemistry, an Advanced Treatise*, 2nd Ed., Wiley, New York, 1953, pp. 1259-1292.

- Crick, F. H. C., "The Genetic Code," *Sci. Am.*, **207** No. 4, 66-74 (Oct., 1962).
 Huisgen, R., "1,3-Dipolar Cycloadditions," *Proc. Chem. Soc.*, **357** (1961).
 Loring, H. S., *Ann. Rev. Biochem.*, **13**, 295 (1944).
 Nirenberg, M. W., "The Genetic Code: II," *Sci. Am.*, **208** No. 3, 80-94 (March, 1963).
 Steele, C. C., "Chlorophyll," in H. Gilman, *Organic Chemistry, an Advanced Treatise*, Vol. II, Wiley, New York, 1953, pp. 1293-1314.
 Wiley, R. H., "Heterocyclic Chemistry," in H. Gilman, *Organic Chemistry, an Advanced Treatise*, Vol. IV, Wiley, New York, 1953, pp. 623-900.

QUESTIONS AND PROBLEMS

1. Show by use of formulas or diagrams accompanied by verbal explanation that you know what is meant by the following terms.

- | | |
|---------------------------|------------------|
| a. heterocyclic | f. porphyrins |
| b. alicyclic | g. bile pigments |
| c. condensed heterocycles | h. nucleic acids |
| d. carbocyclic | i. nucleotides |
| e. isosteres | j. nucleosides |

2. Write structural formulas for the compounds named below. Where tautomers are expected, write the formulas of the most important tautomeric forms.

- | | |
|-------------------------|-----------------------------------|
| a. 2,3-epoxybutane | f. 5-methyl-2-furfural |
| b. 1,3,4-thiazolone | g. 2,2-dimethylazetidine |
| c. 4-methyl-1,3-dioxane | h. 1,3-diazin-2-ol |
| d. benzo[c]thiophene | i. naphtho[2.1-b]furan |
| e. benz[c,d]indole | j. 2H-pyrrolo[3.2.1-i,j]quinoline |

3. Write structural formulas for 5-methylcytosine, caffeine, theobromine, and theophylline.

4. Outline the synthesis of the compounds listed below from the suggested starting materials. Use structural formulas for organic raw materials, both intermediates and products. Indicate essential reagents and conditions insofar as they are general for the type of synthesis.

- 2,4,5-trimethyl-1,3-dioxole from 2-butene
- 2,5-dimethylfuran from ethyl acetoacetate
- 2,5-dimethyl-1,3-oxazole from acetic acid
- amytal (5-isoamyl-5-ethylbarbituric acid) from diethyl malonate, ethanol, isoamyl alcohol, and urea
- hexahydro-1,3-diazin-2-one from cyclopropane and urea
- dibenzo[a,c]phenazine from phenanthrene and *o*-nitrobenzoic acid
- diethyl 3,5-dimethylpyrrole-2,4-dicarboxylate from ethyl acetoacetate
- 3-methyl- Δ^2 -1,2-diazetidine from acetal
- 1-*p*-bromophenyl-3-methyl-5-pyrazolone from benzene, ethanol, and acetic acid
- 2,4,5-tri(diphenylmethyl)-1,3-dioxolane from 1,1,4,4-tetraphenyl-2-butene

43

Physiological Action and Molecular Constitution

Physiological activity in a compound is due to the engagement of the compound in the chemical reactions responsible for the functioning of a living cell. Such a substance may be manufactured by the organism for its own use, may be a necessary or useful material taken into the organism from its environment, or may be a nonessential or detrimental material brought into the organism.

43-1 VITAMINS

A vitamin is an organic material an organism must obtain in its diet in minute amounts. A tabulation of some vitamins, their structures, and their functions is given in Table 43-1. Other vitamins and provitamins have been mentioned elsewhere (§39-3B, §41-2B; Table 41-3). Vitamin precursors or *provitamins* are compounds that have no vitamin activity themselves, but which are converted into vitamins in the organism.

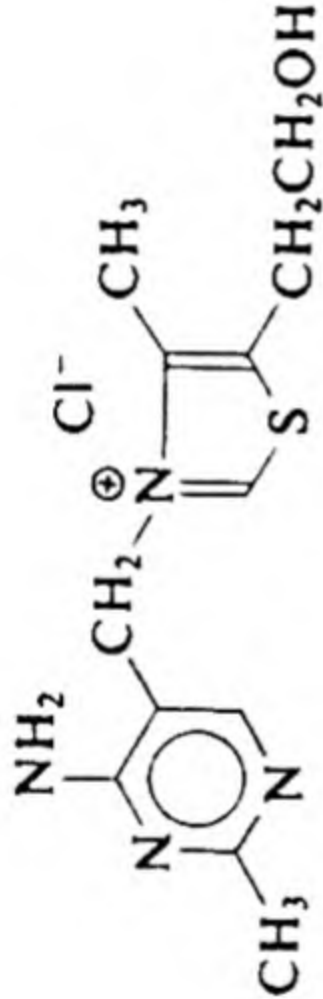
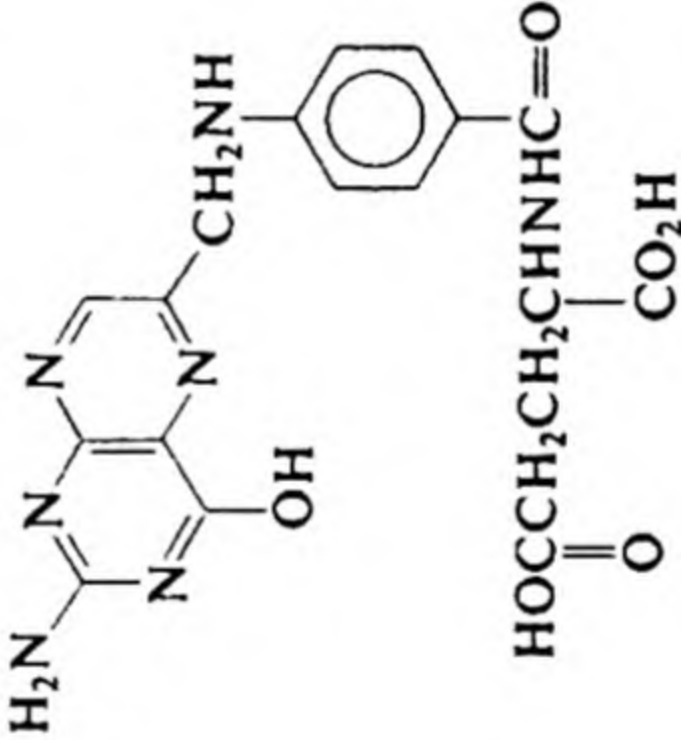
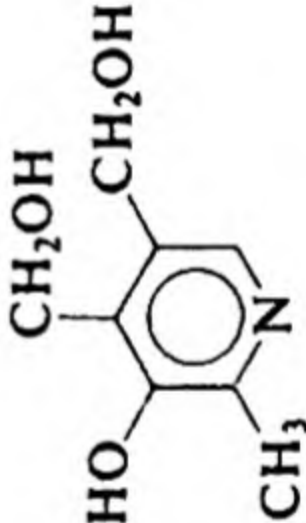
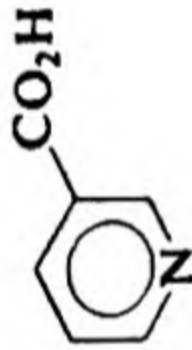
Most vitamins are utilized as portions of coenzymes, (§39-3B). Both functional groups and molecular shape (steric factors) fit a vitamin molecule for a specific biochemical function.

43-2 HORMONES

Hormones are potent regulatory substances manufactured in vertebrates by the endocrine glands and in plants by the buds and leaf tips. Animal hormones belong to three main types of compounds. These are the proteins and polypeptides, the steroids, and a few relatively simple catechol derivatives. It is quite probable that all hormones act in conjunction with proteins. However, a hormone is considered to be the simplest material that shows the physiological activity of the hormone in the absence of the gland that produces it. Like vitamins, hormones may participate in enzyme activity.

Names and functions of some representative animal hormones are given in Table 43-2 and were mentioned in §41-2-§41-2B where steroid hormones were discussed.

TABLE 43-1. Vitamins and Their Functions

Name	Formula	Function
Vitamin B ₁ Thiamine		Pyrophosphate derivative is cocarboxylase, which controls decarboxylation
Vitamin B ₉ Folic Acid Pteroylglutamic Acid		As "active formate," acylation
Vitamin B ₆ Pyridoxine		As pyridoxal phosphate in transamination
Nicotinic Acid (Niacin) a B vitamin		As amide in oxidation coenzymes

Vitamin B₁₂
Cyanocobalamin

Pernicious anemia preventive; trans-
methylation. Resembles a por-
phyrin, but differs in two respects:
four pyrrole rings instead of four
pyrrole rings, and one missing
methine carbon, lower right cor-
ner

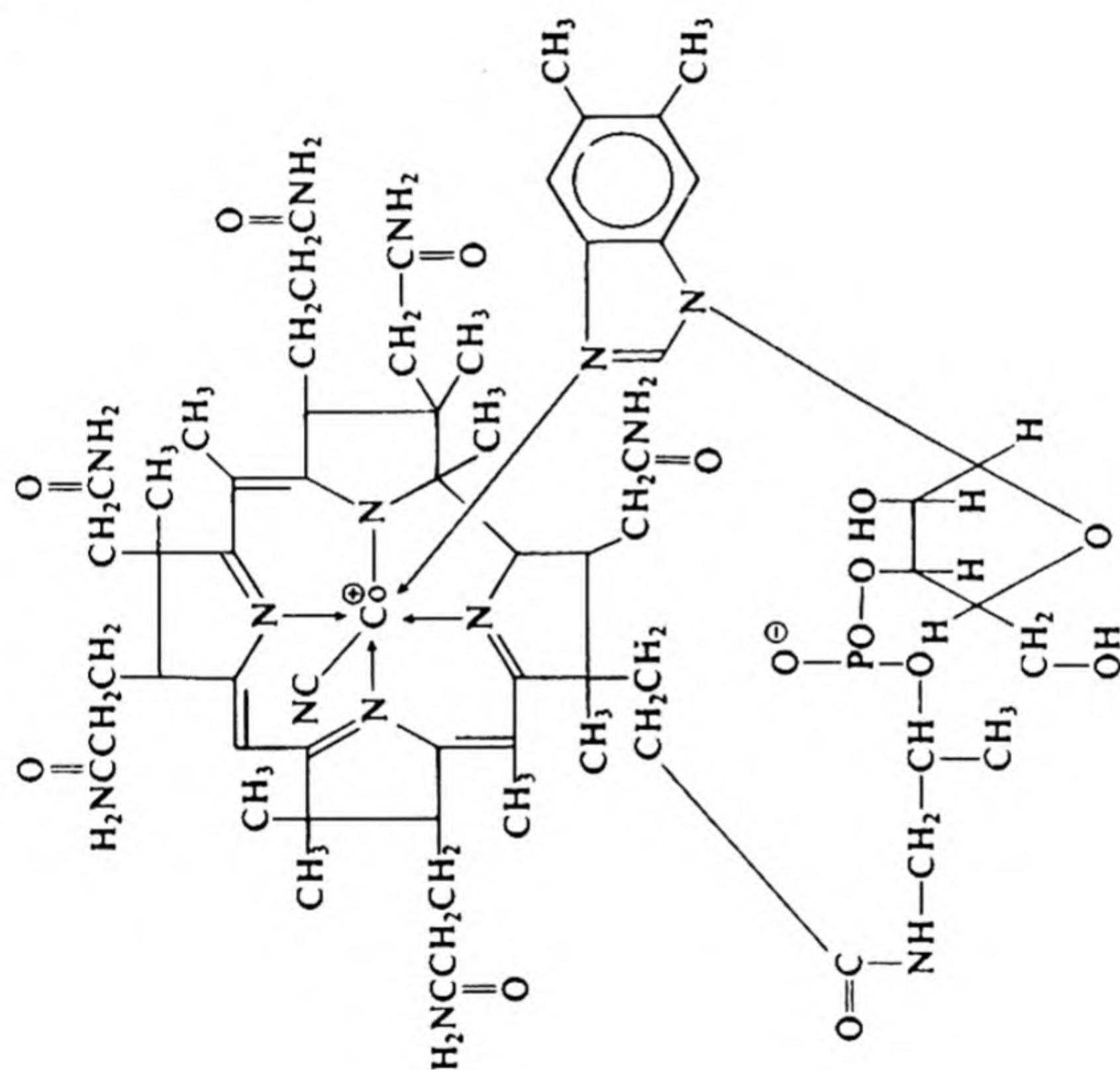


TABLE 43-1. Vitamins and Their Functions (cont.)

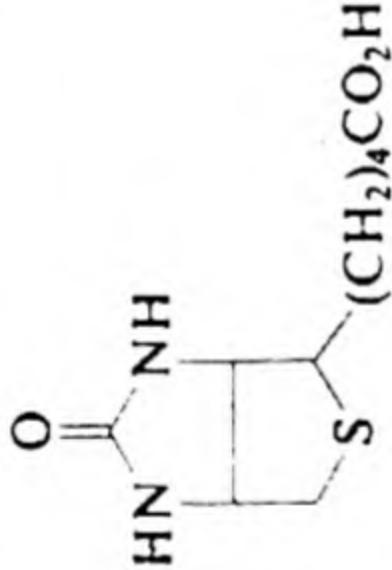

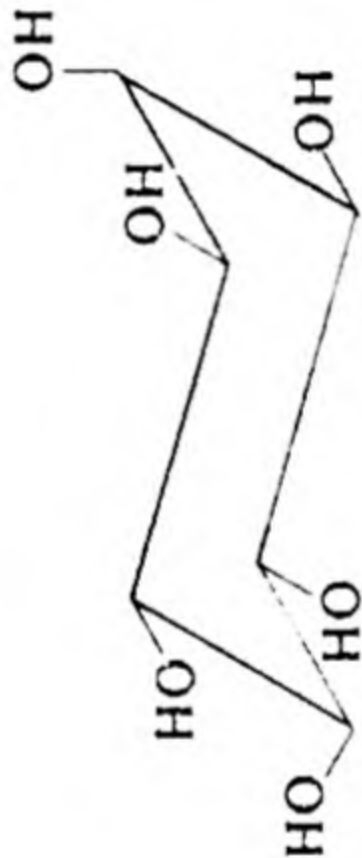
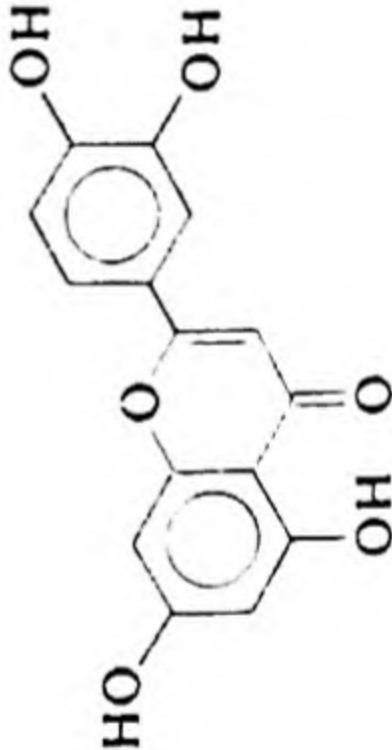
Name	Formula	Function
Biotin (a B vitamin) Coenzyme R		In a carboxylase
<i>p</i> -Aminobenzoic Acid		Probably as portion of folic acid
Inositol		Possibly as phosphoinositides; growth
Choline	$\text{HOCH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_3\text{X}^-$	As lecithin or free; source of methyl groups; nerve signal transmission
Vitamin P Eriodictiol Citrus bioflavonoid		Controls capillary permeability

TABLE 43-1. Vitamins and Their Functions (cont.)

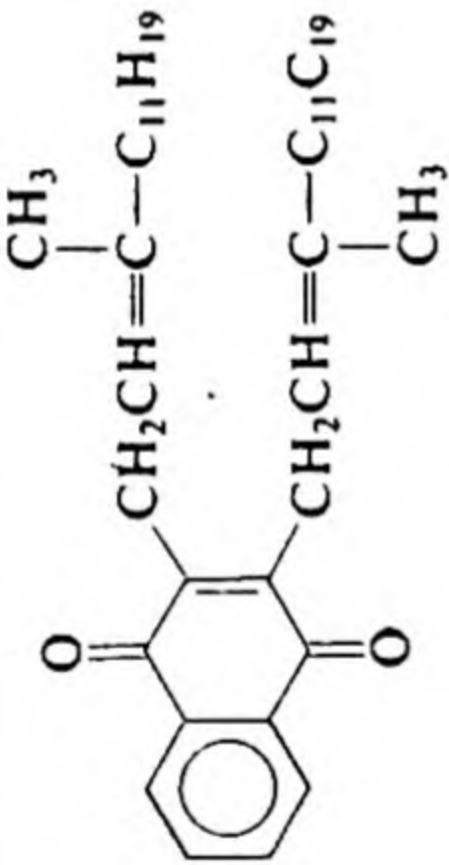
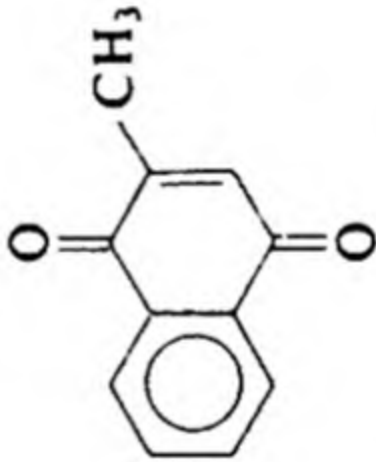
Name	Formula	Function
Vitamin K ₂		
2-Methyl-1,4-naphthoquinone (Synthetic Vitamin K)		Antihemorrhage activity

TABLE 43-2. Representative Animal Hormones and Their Functions

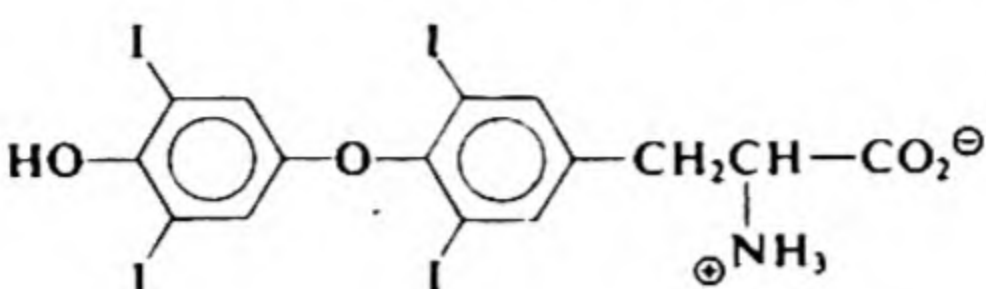
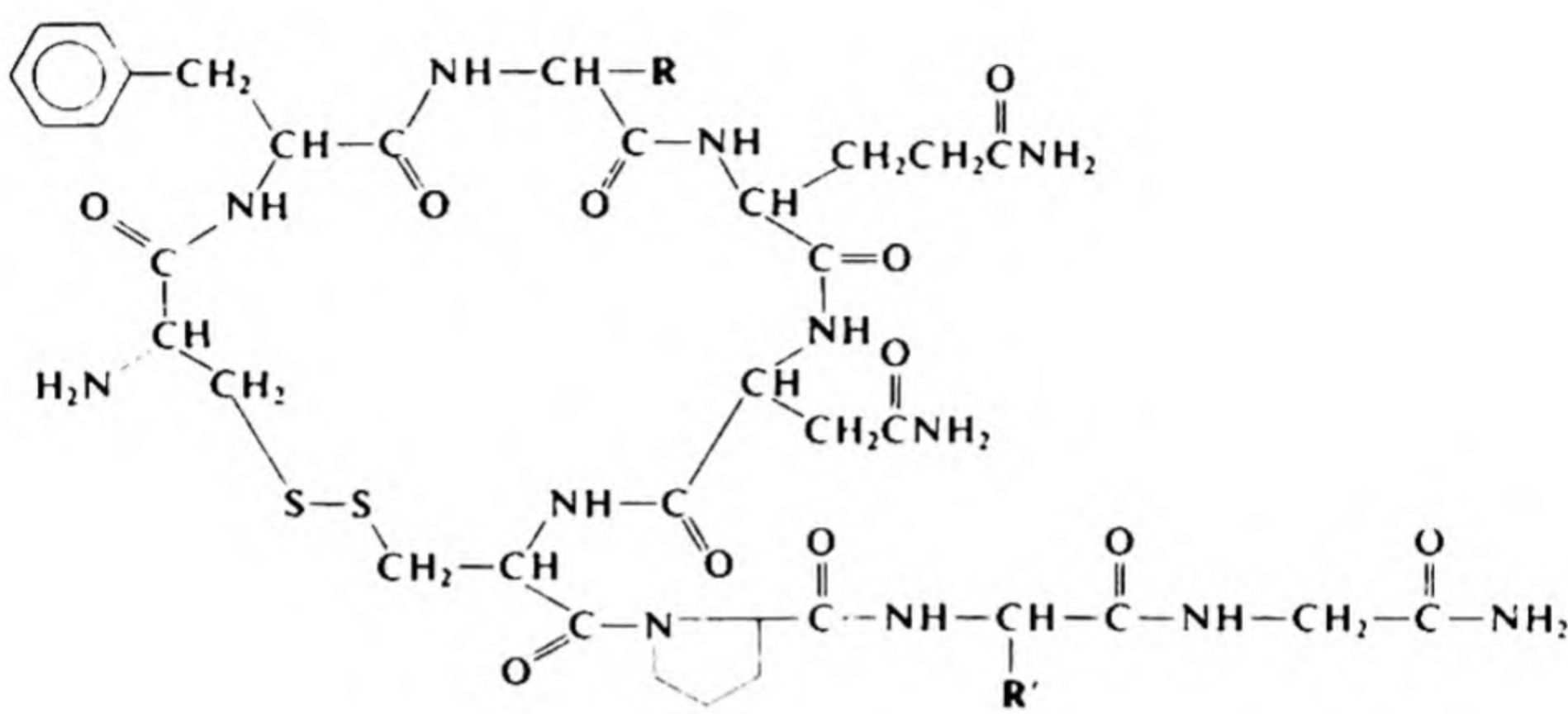
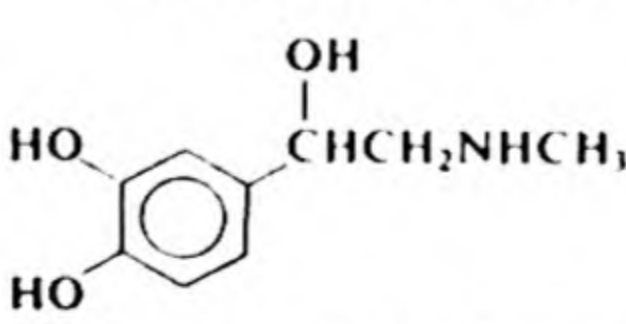
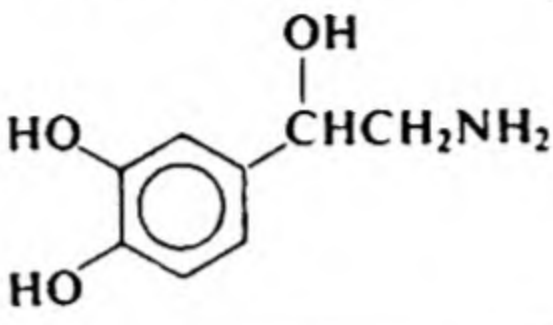
Name	Formula	Function
AMINO ACID AND POLYPEPTIDE HORMONES		
L-Thyroxine		Controls metabolism rate
		
Vasopressin	<p>$R = \text{CH}_2 - \text{C}_6\text{H}_5$</p> <p>$R' = \text{CH}_2\text{CH}_2\text{CH}_2\text{NHCNH}_2 \text{ (beef)}$ $\quad \quad \quad \parallel$ $\quad \quad \quad \text{NH}$</p> <p>or $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2 \text{ (hog)}$</p>	Blood pressure regulator
Oxytocin	<p>$R = \text{CH}(\text{CH}_3)\text{C}_2\text{H}_5$</p> <p>$R' = \text{CH}_2\text{CH}(\text{CH}_3)_2$</p>	Birth and lactation hormone
Insulin	See §39-2E(1), Formula V	Hexose utilization and storage
CATECHOL HORMONES		
Epinephrine Adrenaline		Vasoconstrictor, promotes rapid hexose metabolism

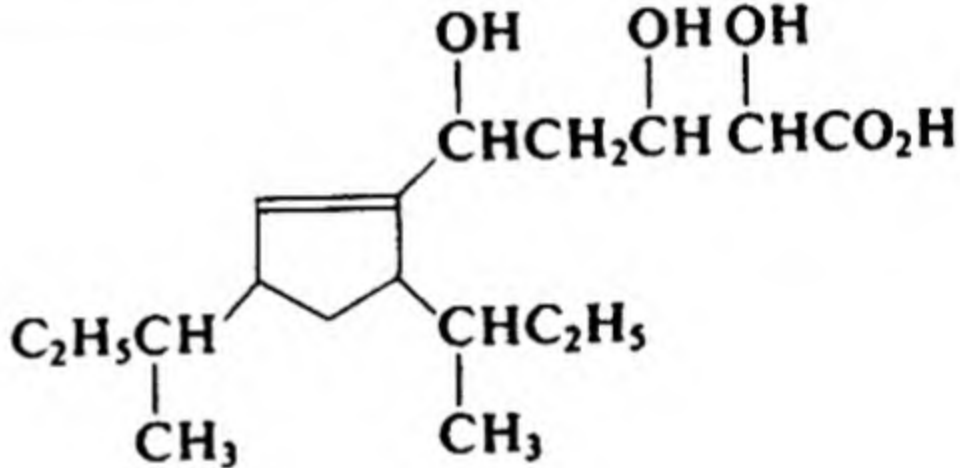
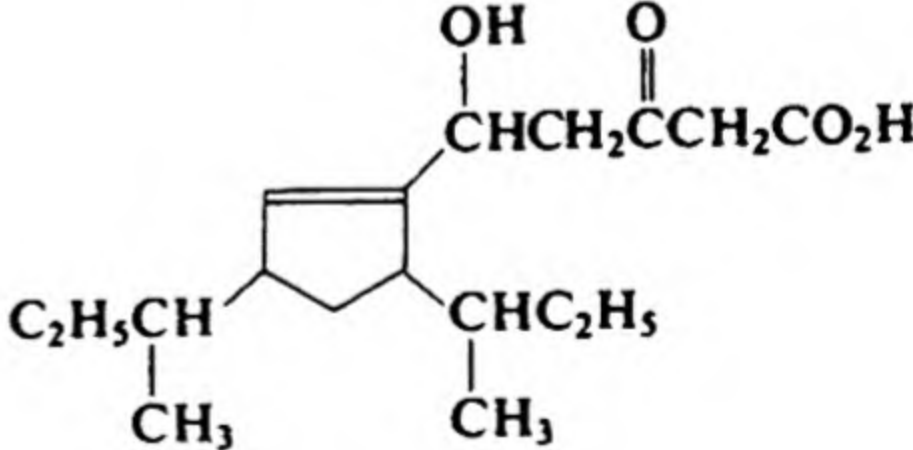
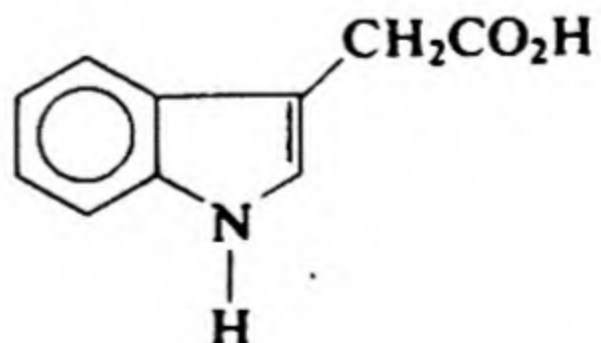
TABLE 43-2. Representative Animal Hormones and Their Functions (cont.)

Name	Formula	Function
CATECHOL HORMONES (cont.)		
Norepinephrine		Vasoconstrictor, promotes rapid hexose metabolism

A. Plant Hormones

Several growth regulators have been isolated from plants. The compounds responsible for growth stimulation, called *auxins*, are given in Table 43-3.

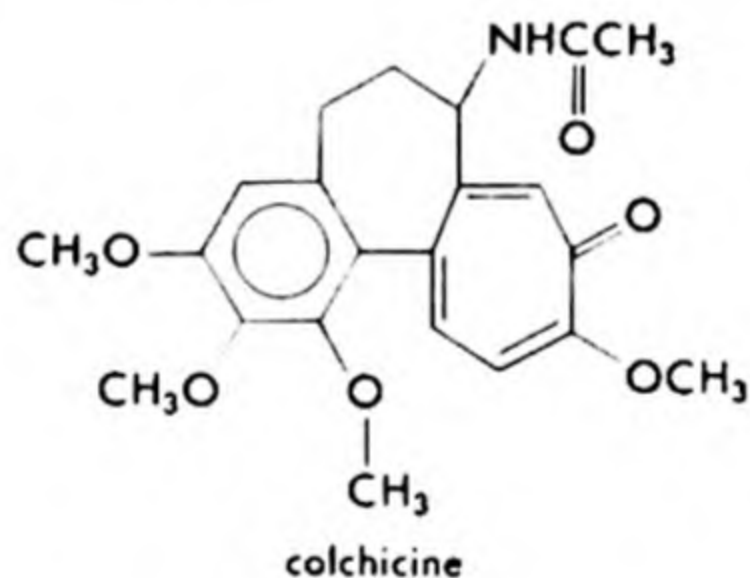
TABLE 43-3. Natural Plant Growth Promoters (Auxins)

Name	Structure
Auxin A	
Auxin B	
Heteroauxin Indole-3-acetic Acid	
Traumatic Acid 2-Dodecenedioic Acid	$\text{HOCOCH}=\text{CH}(\text{CH}_2)_8\text{CO}_2\text{H}$

B. Synthetic Auxins

Many synthetic compounds also radically affect plant growth. Auxin activity is shown by many compounds which have an unsaturated ring system with an acid side chain in which the carboxyl group is separated from an aromatic ring by at least one carbon atom. Auxin activity is shown by derivatives of cyclopentane, benzene, naphthalene, anthracene, indene, indole, and benzofuran. Both branched and continuous side chains show activity. Side chains may be attached to the ring by an ether linkage. Typical synthetic auxins and their major uses are given in Table 43-4.

A compound more fundamental in its effects on plants than any of the auxins and antiauxins is colchicine, an alkaloid obtained from the autumn crocus. Colchicine has the interesting property of arresting cell mitosis at the stage just after division of the chromosomes. It dissolves the spindles connecting the chromosomes, resulting in a cell with double the original number of chromosomes. By treating growing buds, roots, or sprouts with a dilute solution of colchicine for the proper length of time, plants with part or all of their tissues converted to polyploid (multiple chromosomal) cells can be produced. Many new plant varieties have been developed by colchicine treatment followed by appropriate hybridization.



Colchicine contains a *tropone* ring, another nonbenzenoid aromatic system. The seven carbon atoms in the ring share six π electrons and are

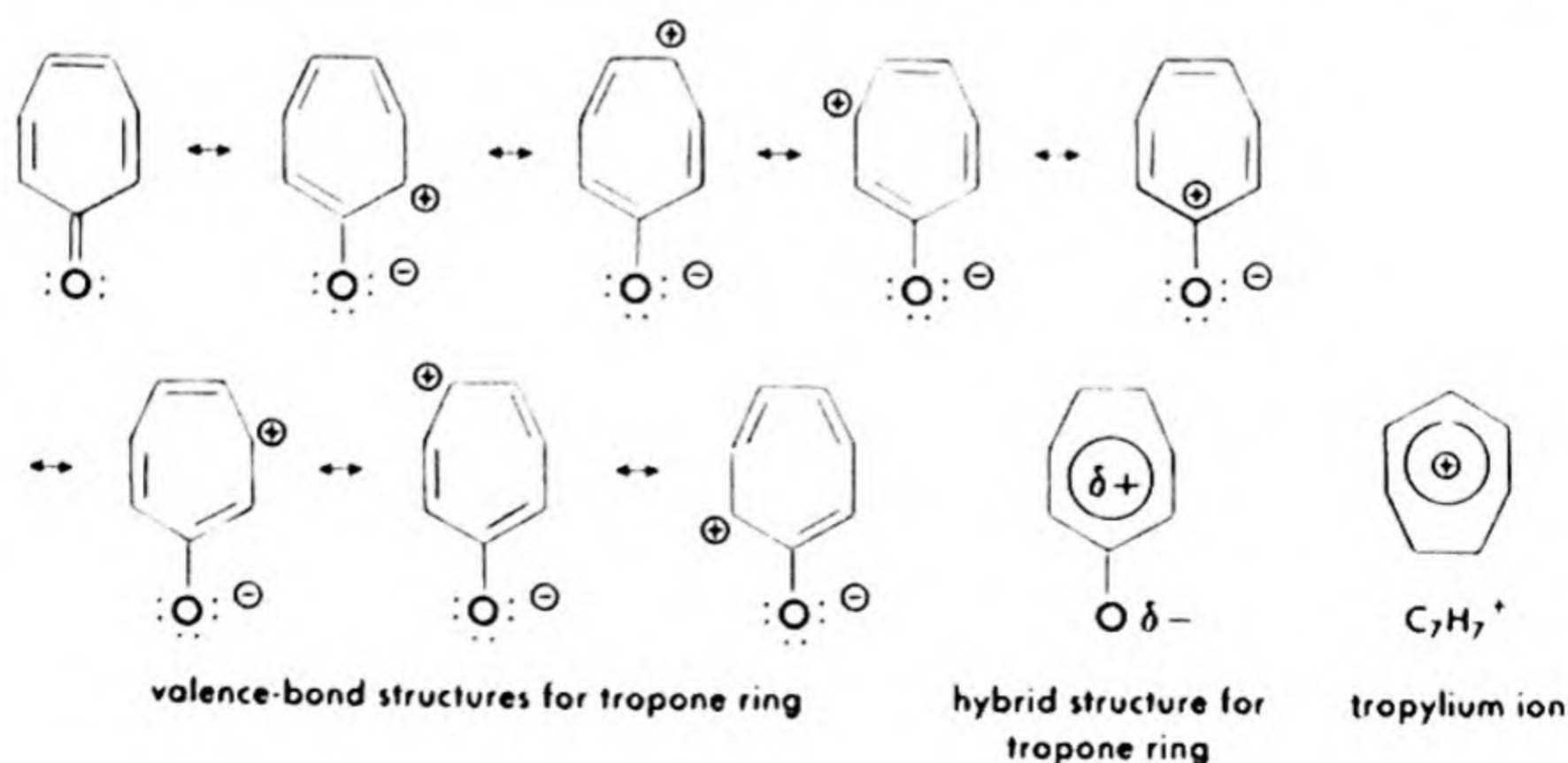
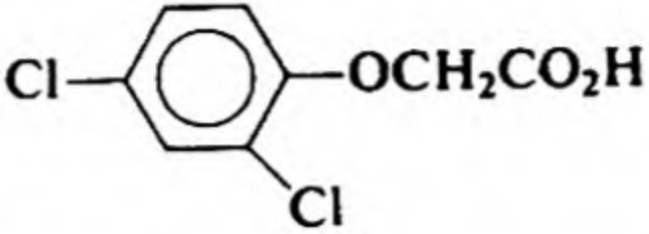
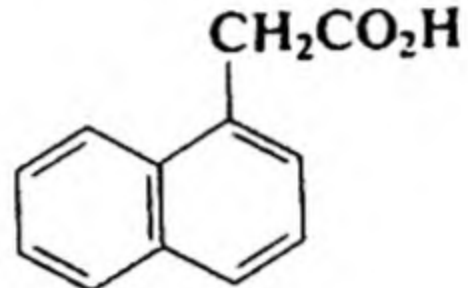
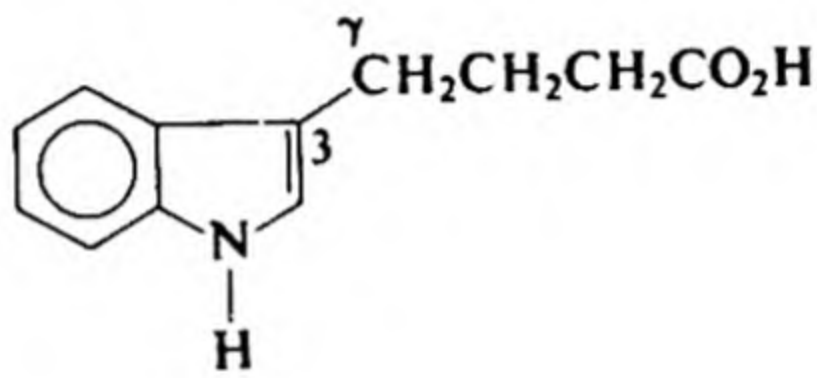
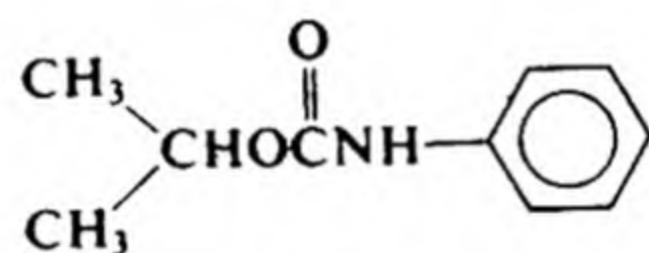
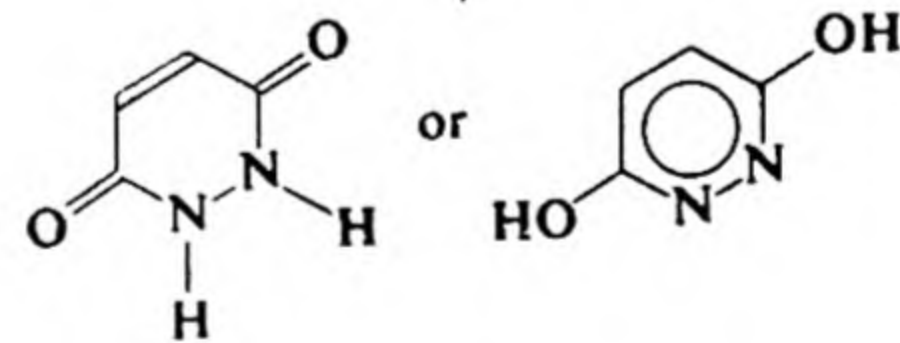
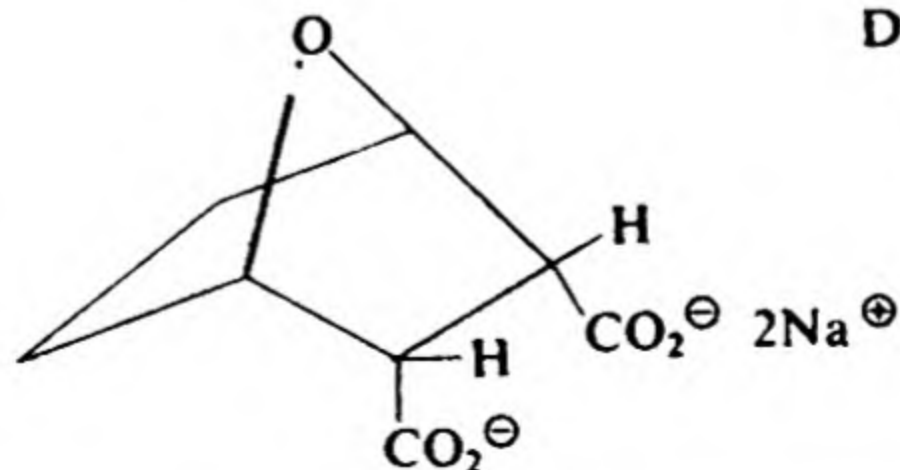


TABLE 43-4. Synthetic Auxins and Their Agricultural Uses

Name	Structure	Use
2,4-D 2,4-Dichloro- phenoxyacetic Acid		Selective herbicide (broad leaved plants)
2,4,5-T	2,4,5-Trichlorophenoxyacetic Acid	Selective herbicide
Naphthalene- 1-acetic Acid		Prevents fruitdrop
γ -Indole-3- butyric Acid		Root growth promoter
IPC Isopropyl <i>N</i> -phenyl- carbamate		Selective grass killer
Chloro IPC	Isopropyl <i>N</i> - <i>m</i> -chlorophenyl carbamate	Selective grass killer
Maleic hydrazide		Sprouting inhibi- tor (antiauxin). An antiauxin is a plant growth regulator which retards growth or opposes aux- in activity.
Endothal Sodium 3,6- endoxohexa- hydrophthalate		Defoliant

therefore considered theoretically by a molecular orbital treatment similar to benzene. The tropylium ion, which also has six π electrons, is a related aromatic system. It is a very stable carbonium ion. Several of its salts have been isolated.

43-3 PESTICIDES

Insects and fungi account for well over half the cost of lost crops and deteriorated property. Additional large economic problems are weed control and rodent control. Eradication of the pests responsible for these afflictions by selective poisons is a major medical and economic consideration.

Poisoning, like drug action, results from interruption of or interference with metabolism. The difference is in the extent of interference. The poison completely stops the functioning of cells, or, in higher organisms, enough critical tissues to cause death. Deadly poisons are those that are fatal in doses of a few milligrams or less per kilogram of body weight. Pesticides have been mentioned frequently elsewhere (§19-3, §29-1E, §40-3C, and Table 42-4): Some further interesting examples are given in Table 43-5.

TABLE 43-5. Representative Pesticides

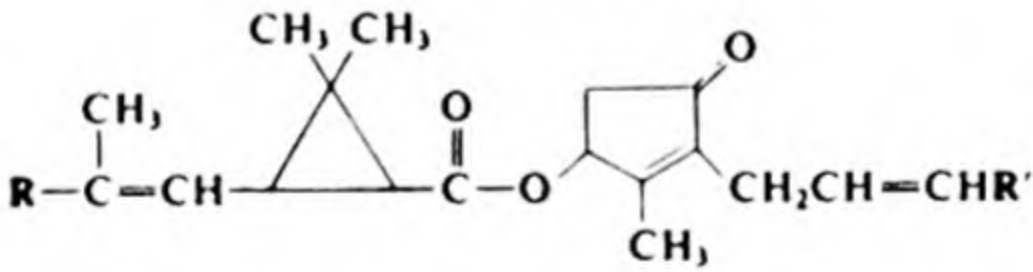
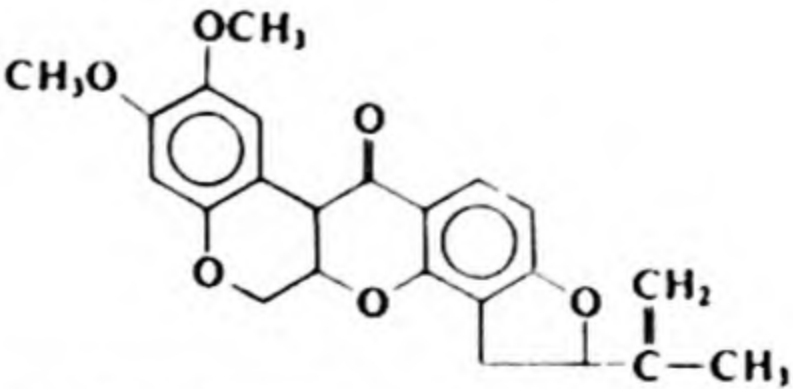
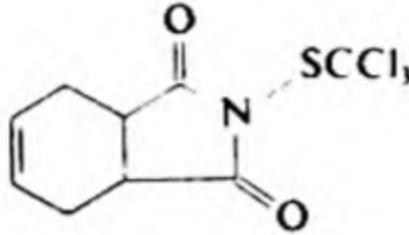
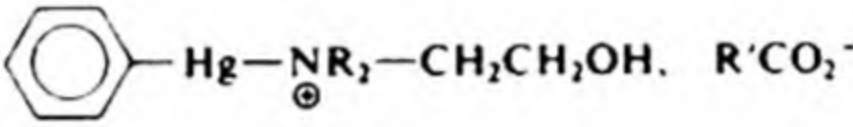
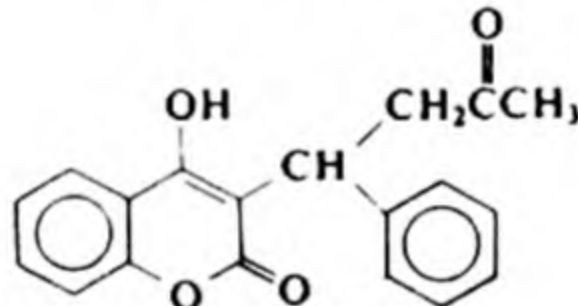
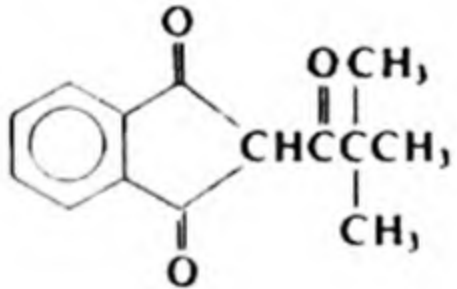
Name	Structure	Comments
INSECTICIDES		
Pyrethrins		Effective ingredients in pyrethrum; Source is the pyrethrum chrysanthemum, native to Japan
I	$R = \text{CH}_3, \quad R' = \text{CH}=\text{CH}_2$	
II	$R = \text{CH}_3\text{OC}(=\text{O})$ $R' = \text{CH}=\text{CH}_2$	
Cinerin I	$R = \text{CH}_3, \quad R' = \text{CH}_3$	
Cinerin II	$R = \text{CH}_3\text{—O—C}(=\text{O})$ $R' = \text{CH}_3$	
Allethrin	$R = \text{CH}_3, \quad R' = \text{H}$	Synthetic
Rotenone		Component of derris roots

TABLE 43-5. Representative Pesticides (cont.)

Name	Structure	Comments
INSECTICIDES (cont.)		
TEPP Tetraethyl Pyrophosphate	$ \begin{array}{c} (\text{C}_2\text{H}_5\text{O})_2\text{P}-\text{O}-\text{P}(\text{OC}_2\text{H}_5)_2 \\ \downarrow \quad \quad \downarrow \\ \text{O} \quad \quad \text{O} \end{array} $	Prepared by treating triethyl phosphate with POCl_3 ; very toxic
Parathion	$ \begin{array}{c} (\text{C}_2\text{H}_5\text{O})_2\text{P}-\text{O}-\text{C}_6\text{H}_4-\text{NO}_2 \\ \downarrow \\ \text{S} \end{array} $	Very toxic; made from sodium <i>p</i> -nitrophenoxide and diethylthiophosphoryl chloride
Malathion	$ \begin{array}{c} (\text{CH}_3\text{O})_2\text{P}-\text{S}-\text{CH}(\text{COOC}_2\text{H}_5)_2 \\ \downarrow \\ \text{S} \end{array} $	Least toxic to mammals of the phosphorus insecticides; made from ethyl maleate and <i>O,O'</i> -dimethyl dithiophosphate
FUNGICIDES		
Chloranil		Used for seed treatment
Dichlone		Used for seed treatment; made by chlorinating 1,4-diaminonaphthalene-2-sulfonic acid
Pentachlorophenol		Used as wood preservative
Dithiocarbamates	$ \left(\begin{array}{c} \text{R}-\text{N}-\text{C}-\text{S}^\ominus \\ \quad \quad \parallel \\ \quad \quad \text{S} \end{array} \right)_n \text{M}^{n+} $	Prepared by treating 2°-alkylamines with CS_2 and NaOH
Thiuram Disulfides	$ \begin{array}{c} \text{R}_2\text{NCSSCNR}_2 \\ \parallel \quad \parallel \\ \text{S} \quad \text{S} \end{array} $	Prepared by oxidizing dithiocarbamates

TABLE 43-5. Representative Pesticides (cont.)

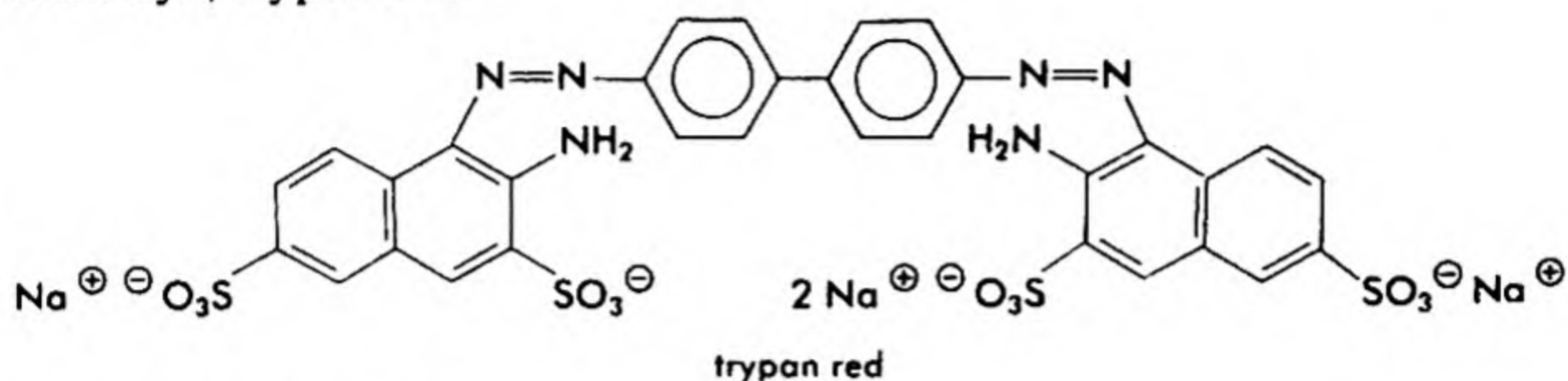
Name	Structure	Comments
FUNGICIDES (cont.)		
Thiuram Monosulfides	$\begin{array}{c} R_2NCSCNR_2 \\ \quad \\ S \quad S \end{array}$	Made by treating thiuram disulfides with KCN
Captan		Made from tetrahydrophthalimide and trichloromethyl mercaptan
Organomercury Compounds		Used on fruit trees before fruit set
RODENTICIDES		
Warfarin		Anticoagulant; requires repeated ingestion; compare dicoumarol (§42-1G)
Pival 2-Pivalyl-1,3-indanedione		Anticoagulant

Frequently, it is more satisfactory to repel pests rather than try to kill them. Insect repellants, for example, are used on the skin to avoid bites in locations where it would be impracticable to kill all the insects. Several effective odorless (to man) compounds are in use, among them *N*-butylacetanilide, *N,N*-diethyl-*m*-toluamide, butoxypropylene glycol, 2-ethyl-1,3-hexanediol, and methyl phthalate.

43-4 CHEMOTHERAPY

Chemotherapy is the use of drugs selectively to inhibit growth of parasitic organisms and thus cure a disease. While the use of drugs medicinally for many purposes is an ancient art, the particular branch of pharmacy known as chemotherapy is relatively recent. As a science,

chemotherapy began with the efforts of Paul Ehrlich at the start of the twentieth century to discover chemical compounds that are toxic to pathogenic organisms but nontoxic to the host. His first success, in 1907, was the curing of mice inoculated with a form of trypanosomiasis, by use of a bisazo dye, trypan red.

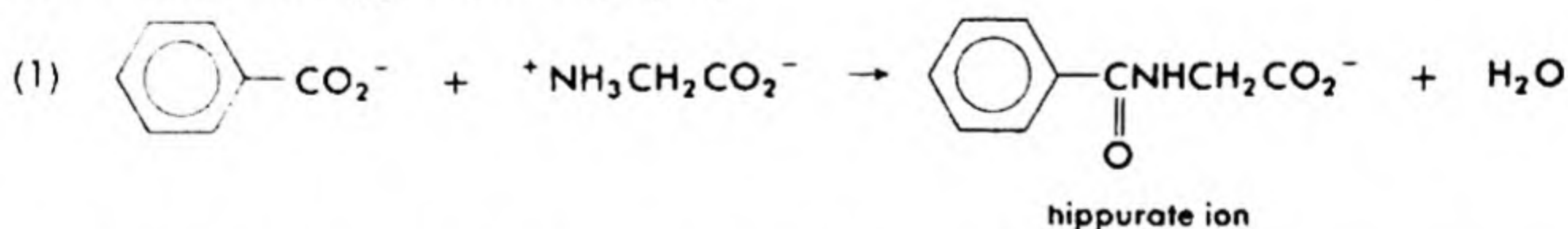


A. Mechanisms of Chemotherapeutic Action

The active microbial defenses of the body are chemical and biological in action. The body manufactures *antibodies* to combat specific antigens, usually toxic, manufactured by infecting organisms. Both the antibodies and the antigens are proteins. The biological defense is the engulfing of microbes by leucocytes.

Antitoxins are seral antibodies which neutralize specific disease toxins. Vaccines are devitalized disease organisms which, upon administration, stimulate the body to manufacture antibodies in defense against the disease.

Since a chemotherapeutic agent is a foreign agent, the body attempts to get rid of it as quickly as possible, by altering it chemically, either to make it less toxic or to make it more soluble and more easily excreted. The means by which the body does this are, variously, oxidation, amination, deamination, and acylation. For example, benzoic acid is detoxified by conversion to hippuric acid (eq. 1).



Action of drugs to stop metabolic processes belongs to these categories: disruption of cellular structure by surface activity, inhibition of enzyme activity, competitive metabolite antagonism, osmotic force changes, changes in ionic concentrations and changes in redox potential. Naturally, these effects are detrimental to the host as well as to the parasite. Choice of a chemotherapeutic agent requires toxicity to the parasite to be substantially higher than that to the host.

(1) *Surface Active Agents.* Most antiseptics operate by changing the surface characteristics of cell membranes, thus disrupting the cell so that cell constituents are no longer retained in the necessary organization.

Structural changes show regular effects on bacteriostatic effectiveness of

hydroxy compounds. Phenols are more effective than alcohols. Increasing the length of alkyl chains increases effectiveness up to the point that diminishing solubility takes over. Increasing number of hydroxy groups decreases effectiveness up to the point that diminishing solubility takes over. Increasing number of hydroxy groups decreases effectiveness, but also decreases toxicity to host. Substituent chlorine atoms and nitro groups increase effectiveness.

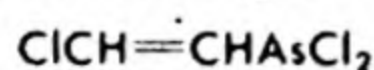
(2) *Metabolite Antagonists.* Substitute coenzymes or substrates containing groups similar to, but not enough like, the normal coenzyme or substrate groups can be provided to compete with the normal agents.

The normal metabolite, either coenzyme or substrate, must be essential to metabolism. A substitute metabolite might behave in any one of several ways. The substitute may be so like the natural metabolite as to replace it without ill effects, so different from the natural metabolite as to be incapable of either replacement or competition, or enough like the natural metabolite to enter the series of reactions necessary to metabolism, but different enough not to be able to replace the natural metabolite all the way. The last situation is the one in which competitive inhibition can occur. Some examples are given in Table 43-6. Compounds which appear in the *Competitive Activity* column of Table 43-6 show promise of use as bacterial inhibitors.

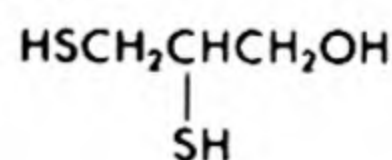
A characteristic of antimetabolite inhibitors is that, in many cases, large amounts of the normal metabolite nullify the effects of the inhibitor. Both materials follow the mass action law in arriving at an equilibrium, favorable or unfavorable to growth, depending on the relative proportions of each present.

(3) *Enzyme Neutralizers.* Compounds which interfere with enzyme activity by blocking their reactive groups are common and abundant. Some are so powerful in their effects as to be universal poisons valueless for chemotherapeutic use. For example, heavy metal ions tie up mercapto groups in coenzyme A and similar coenzymes which participate in redox. Use of arsenic compounds as war gases is illustrative. Carbon monoxide, cyanide ions, and azide ions bind iron in porphyrins, blocking the activity of cytochromes as well as hemoglobin.

A characteristic of this type of drug action is that it can be counteracted by an antidote which ties up the poison more effectively than the enzyme does. Thus, an antidote to poisoning by Lewisite, a war "gas," is BAL (British Anti-Lewisite), which provides mercapto groups that prevent the arsenic from affecting enzymes with sensitive groups.



dichlorochlorovinylarsine
Lewisite



1,2-dithioglycerol
BAL

TABLE 43-6. Effects of Substitute Compounds on Metabolism^a

Essential Metabolite	Similar Activity	Competitive Activity	Little or No Activity
<chem>[NH3+][c1ccc(cc1)C(=O)[O-]]</chem> <i>p</i> -aminobenzoic acid (a vitamin)	<chem>[NH3+][c1ccc(cc1)C(=O)[O-]]</chem> <chem>[NH3+][c1ccc(cc1)C(=O)O</chem>	<chem>[NH3+][c1ccc(cc1)C(=O)[O-]</chem> <chem>[NH3+][c1ccc(cc1)S(=O)(=O)NHR</chem>	<chem>([CH3])2N[c1ccc(cc1)C(=O)[O-]]</chem> <chem>[NH3+][c1ccc(cc1)CC(=O)[O-]</chem>
<chem>CC(C)[C@H](O)C(=O)CNC(=O)CCO</chem> pantothenic acid (a vitamin)	<chem>CC(C)[C@H](O)C(=O)CNC(=O)CCO</chem> <chem>CC(C)[C@H](O)C(=O)CNC(=O)CCO</chem>	<chem>CC(C)[C@H](O)C(=O)CNC(=O)CCO</chem> <chem>CC(C)[C@H](O)C(=O)CNC(=O)CCO</chem>	<chem>CC(C)[C@H](O)C(=O)CNC(=O)CCO</chem> <chem>CC(C)[C@H](O)C(=O)CNC(=O)CCO</chem>
<chem>Cc1nc(C)nc(C)nc1</chem> thiamin (vitamin B ₁)	<chem>Cc1nc(C)nc(C)nc1</chem> <chem>Cc1nc(C)nc(C)nc1</chem>	<chem>Cc1nc(C)nc(C)nc1</chem> <chem>Cc1nc(C)nc(C)nc1</chem>	<chem>Cc1nc(C)nc(C)nc1</chem> <chem>Cc1nc(C)nc(C)nc1</chem>
<chem>Cc1nc(C)nc(C)nc1</chem> biotin	<chem>Cc1nc(C)nc(C)nc1</chem> <chem>Cc1nc(C)nc(C)nc1</chem>	<chem>Cc1nc(C)nc(C)nc1</chem> <chem>Cc1nc(C)nc(C)nc1</chem>	<chem>Cc1nc(C)nc(C)nc1</chem> <chem>Cc1nc(C)nc(C)nc1</chem>

^aW. A. Sexton, *Chemical Constitution and Biological Activity*, E. & F. N. Spon Ltd., London (1953), pp. 50-51.

B. Antibiotics

Substances produced naturally by living organisms that inhibit the growth of microorganisms are antibiotics. Alexander Fleming was the first to recognize the importance of such inhibition, a discovery which led to the isolation of one of the penicillins from a mold culture by Flory and his students. Some of the important antibiotics of known structure are given in Table 43-7.

TABLE 43-7. Representative Antibiotics

Name	Structure	Comments
Penicillin G Benzyl Penicillin		Most widely used antibiotic
Chloroamphenicol		Now prepared synthetically
Terramycin		One of several tetracycline antibiotics
Streptomycin		One of several glycosidic antibiotics

SUPPLEMENTARY READINGS

Burger, A., "Chemical Structure and Biological Activity," *J. Chem. Educ.* **35**, 142-144 (1958).

- Burger, A., "Rational Approach to Drug Structure," *J. Chem. Educ.* **33**, 362-362 (1956).
- Cheney, L. C., "Antibiotics," in H. Gilman, *Organic Chemistry, an Advanced Treatise*, Vol. III, Wiley, New York, 1953, pp. 533-580.
- De Ong, E. R., *Chemistry and Uses of Pesticides*, Reinholt, New York, 1956.
- Frear, D. E. H., *Chemistry of the Pesticides*, 3rd Ed., Van Nostrand, Princeton, N. J., 1955.
- Ing, H. R., "Some Aspects of Chemotherapy," in H. Gilman, *Organic Chemistry, an Advanced Treatise*, Vol. III, Wiley, New York, 1953, pp. 392-532.
- Ray, R. L., "Alkaloids—the World's Pain Killers," *J. Chem. Educ.* **37**, 451-454 (1960).
- Roderick, W. R., "Structural Variety of Natural Products," *J. Chem. Educ.* **39**, 2-11 (1962).
- Sangster, A. W., "Determination of Alkaloid Structure," *J. Chem. Educ.* **37**, 454-459 (1960).
- Schueler, F. W., Ed., "Molecular Modification in Drug Design," *Adv. Chem. Ser.*, 1964.
- Sexton, W. A., *Chemical Constitution and Biological Activity*, 2nd Ed., Van Nostrand, Princeton, N. J., 1953.

QUESTIONS AND PROBLEMS

1. Show clearly what is meant by each of the following terms. Accompany formulas and diagrams with verbal explanation.

- | | |
|--------------------------------------|-----------------------|
| a. antibiotic | h. drug |
| b. fungicide | i. enzyme neutralizer |
| c. herbicide | j. hormone |
| d. antibody | k. insecticide |
| e. auxin | l. pesticide |
| f. chemotherapy | m. provitamin |
| g. competitive metabolite antagonism | n. rodenticide |
| | o. vitamin |

2. State how chemotherapy and pest control are similar in principle, and in what ways they differ in principle.

3. Show how the following compounds can be prepared from methanol, ethanol, acetic acid, benzene, toluene, naphthalene, furfural, and inorganic reagents. Indicate reagents and essential special conditions. Use structural formulas for organic compounds.

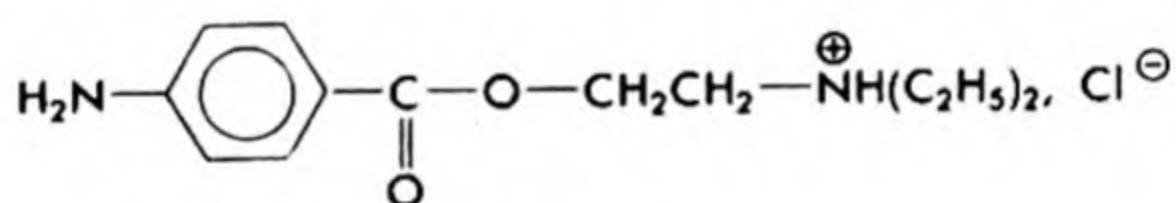
- | | |
|-------------------------------|--------------------------------|
| a. allethrin | f. butoxypropylene glycol |
| b. methoxychlor | g. 2-ethyl-1,3-hexanediol |
| c. parathion | h. dichlone |
| d. malathion | i. zinc diethyldithiocarbamate |
| e. <i>N</i> -butylacetanilide | j. warfarin |

- | | |
|---|------------------------------|
| k. tetraethyl thiuram monosulfide | n. IPC |
| l. captan | o. 2,4,5-T methyl ester |
| m. phenylmercuritriethanol-ammonium acetate | p. endothal |
| | q. naphthalene-1-acetic acid |

4. Show how the following compounds can be prepared from methanol, ethanol, ethyl malonate, benzene, toluene, pyridine, phosgene, and inorganic compounds, including carbon monoxide, alkali cyanides, and the like. Indicate reagents and essential special conditions. Use structural formulas for organic compounds.

- | | |
|--------------------------------|------------------------------|
| a. amytal | e. epinephrine |
| b. nicotinic acid | f. procaine (see Question 5) |
| c. <i>p</i> -aminobenzoic acid | g. chloramphenicol |
| d. oxytocin | h. maleic hydrazide |

5. Compare procaine with cocaine (§42-1H). Indicate the similarities in structural features which may contribute to similar anesthetic properties.



procaine

6. One of the B vitamins (Table 43-1) gave negative results with reducing agents, carbonyl group reagents, and the ninhydrin α -amino acid test and showed little inclination toward hydrolysis by either acid or alkali. It was sensitive to oxidation by ether hydroperoxides and by bromine, both of which reagents destroyed its biological activity. The compound formed a methyl ester.

Drastic treatment of the compound with barium hydroxide in a sealed tube at 140° gave a new compound. This material showed two primary amino groups by Van Slyke analysis. It gave a dibenzoyl derivative and formed the original vitamin again by treatment with phosgene. Permanganate or nitric acid oxidation of the diamino compound gave adipic acid. Treatment of the diamino compound with 9,10-phenanthrenequinone gave either a quinoxaline or dihydroquinoxaline derivative. The absorption spectrum of the product suggested the former.

Curtius degradation of the azide prepared from the vitamin in the usual manner gave an amino derivative which produced no adipic acid upon oxidation. Name and write the structural formula of the vitamin. Write equations for all of the reactions described.



Petroleum Products

44-1 PETROLEUM REFINING

The main uses for petroleum products are fuel, solvents, lubricants, and synthetic chemicals. All of these require refining. This is a complex of processes which begin with physical fractionation and extend to chemical modification.

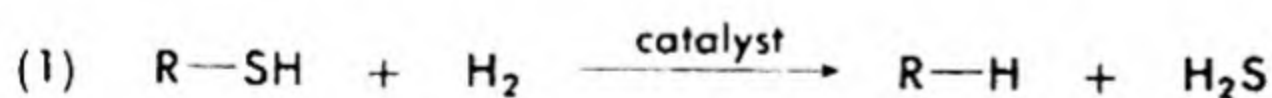
A. Physical Separations

Fractional distillation, solvent extraction, and crystallization play major roles in the separation of materials at several stages in refining processes.

B. Chemical Purification Processes

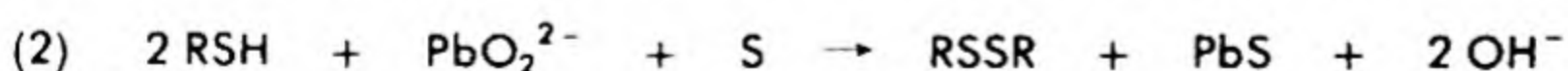
Since sulfur compounds poison catalysts in many of the refining processes and are undesirable in finished products, reduction of sulfur content is often carried out. Four methods of removal are used currently.

Catalytic desulfurization, in which the crude fraction is treated with hydrogen under pressure and in contact with solid catalysts, is used extensively.



A second method is acid treatment. Sulfuric acid is used to dissolve sulfur compounds, as well as nitrogen bases.

A third method utilizes oxidation by heavy metal salts, such as a sodium plumbite-sulfur mixture (*doctor solution*) or cupric chloride. This procedure converts mercaptans to disulfides (eq. 2). It does not reduce the sulfur content, but does remove the unpleasant odor of the thiol.



The fourth method utilizes sodium hydroxide or other bases in aqueous methanol. The mercaptans form water-soluble salts.

Recovery of the sulfur with ultimate oxidation to sulfuric acid is often economically attractive and provides a source of sulfuric acid for other refinery operations.

C. Chemical Modification Processes

In order to convert more of the crude oil to gasoline and to improve the quality of gasoline, several chemical processes have become essential parts of petroleum refining.

The *knock rating* of a gasoline is measured by its performance in a standard engine compared with that of standard compounds, *n*-heptane with a knock rating of zero and 2,2,4-trimethylpentane (called "iso-octane" incorrectly), rated 100. The *octane number*, or knock rating, of a gasoline is defined as the per cent of 2,2,4-trimethylpentane in a mixture with *n*-heptane that gives the same performance as the test gasoline.

Compounds which surpass 2,2,4-trimethylpentane in knock performance are rated on the basis of the power developed when they are used as compared with the power developed by the standard octane. Hence, octane numbers over 100 are based differently than those under 100.

In general, octane number decreases with increasing chain length, increases with increased branching and unsaturation, is higher in aromatic compounds than aliphatic or alicyclic, and increases with length and number of aliphatic side chains on aromatic rings. Greater symmetry of molecules is also a factor. Centrally substituted and centrally unsaturated hydrocarbons have higher octane numbers than 2-methyl or terminally unsaturated hydrocarbons. *Para* dialkyl and symmetrical trialkylbenzenes have the highest octane numbers of the aromatic positional isomers. Octane numbers of cycloalkanes usually lie between those of alkanes and arenes. There are many exceptions to these generalities, however (see Table 44-1 for examples).

(1) *Cracking*. The primary aim of cracking is to convert larger hydrocarbon molecules to those with boiling points in the gasoline range.

Thermal cracking depends on high temperature alone to break down the material. Octane ratings of the products are lower than those of catalytic cracking products. There is much loss of material to the production of coke and gas. Because of these disadvantages, thermal cracking is confined now to those stocks which cannot be cracked catalytically because of high metals content, such as the residuum from certain types of crudes.

Thermal cracking doubtless occurs by a free radical mechanism. Bond rupture is followed by abstraction of hydrogen atoms from other molecules by the radicals formed or by loss of hydrogen or smaller alkyl radicals.

Catalytic cracking has the advantages of better control and higher reaction rate for a given temperature. *Fluid catalytic cracking* (Fig. 44-1) is the most common modern process, since it has the advantage of continuous operation. A fine alumina-silica catalyst which flows like a liquid in the vapor stream moves continuously between the reactor, in which it

TABLE 44-1. Motor Method Octane Numbers of Representative Hydrocarbons^a

C ₆	Octane Number	C ₇	Octane Number	C ₈	Octane Number
MOTOR OCTANE NUMBERS					
hexane	26.0	heptane	0.0	octane	-13.6
2-methylpentane	73.5	3-methylhexane	46.4	2-methylheptane	23.8
3-methylpentane	74.3	3-ethylpentane	69.3	4-methylheptane	39.0
2,2-dimethylbutane	93.4	3,3-dimethyl-		2,2-dimethylhexane	77.4
1-hexene	76.4	pentane	86.6	2,2,4-trimethyl-	
2-methyl-1-pentene	78.9			pentane	100.0
2-methyl-2-pentene	83.0			1-octene	28.7
<i>cis</i> -2-methyl-				<i>trans</i> -4 octene	74.3
2-pentene	84.3				
BLENDING MOTOR OCTANE NUMBERS					
hexane	22	heptane	0.0	octane	-15
benzene	91	toluene	112	ethylbenzene	107
				<i>o</i> -xylene	103
				<i>m</i> -xylene	124
				<i>p</i> -xylene	127

^aC. Boord, "Relation of Properties to Molecular Structure for Petroleum Hydrocarbons," *Progress in Petroleum Technology*, American Chemical Society (1951), pp. 364-370. Reprinted by permission.

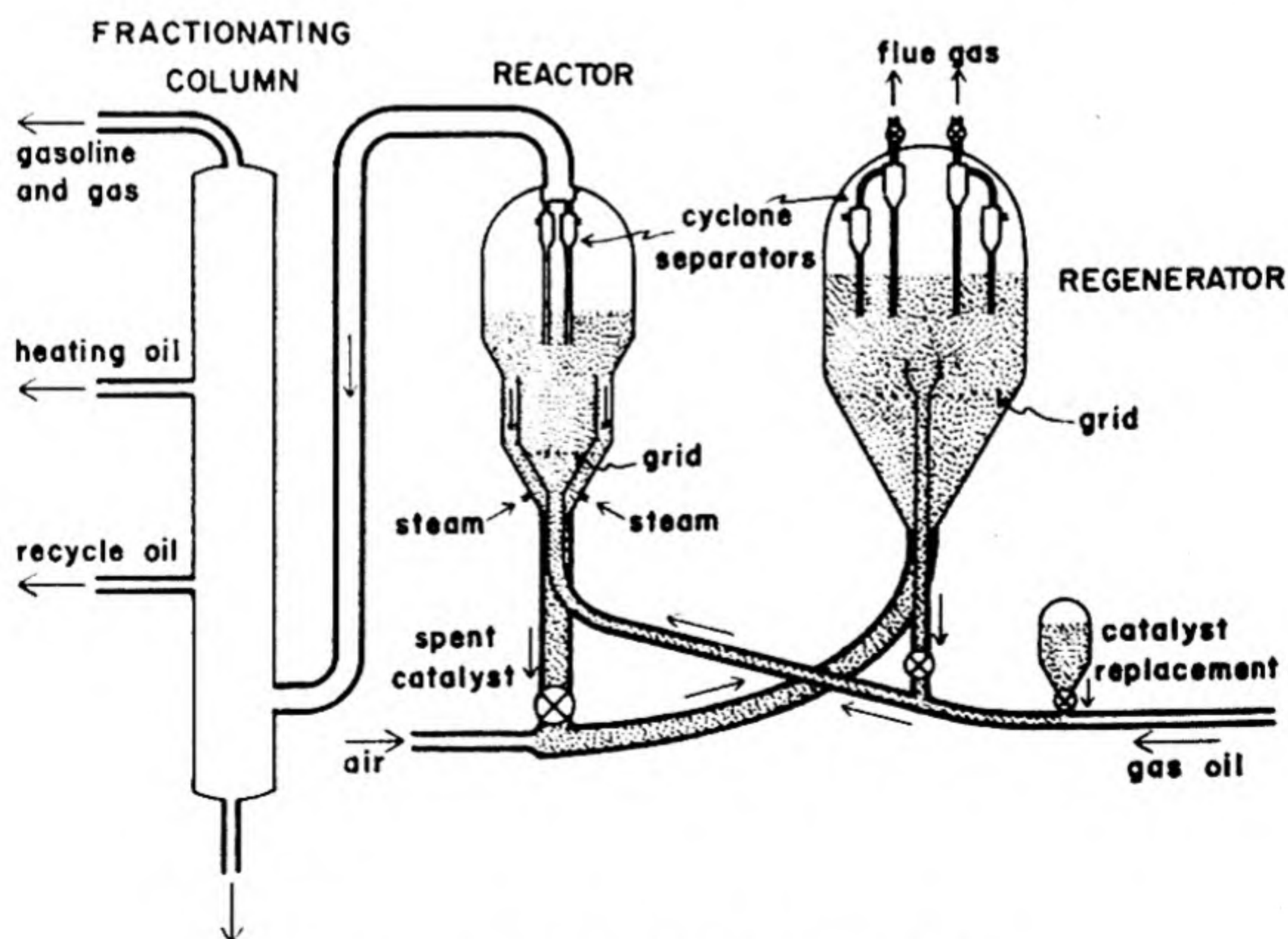
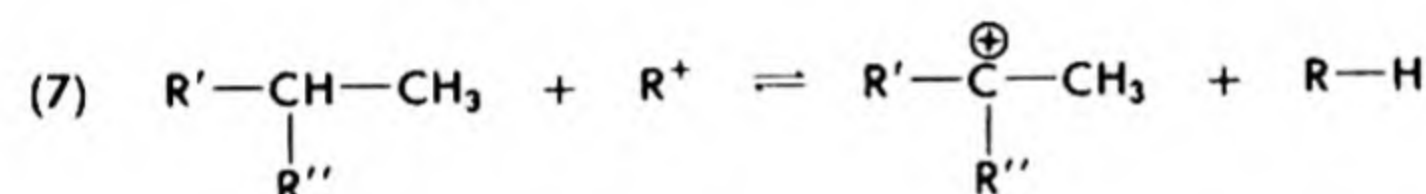
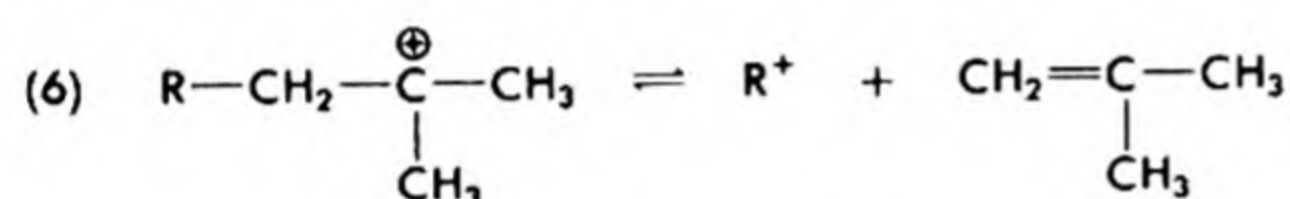
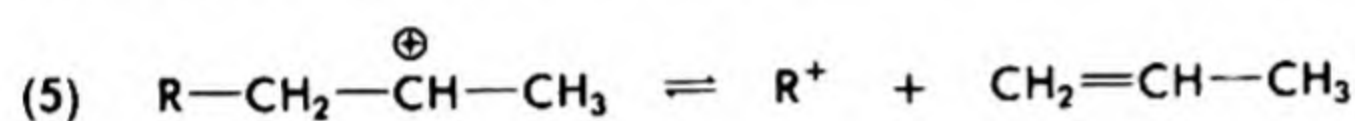
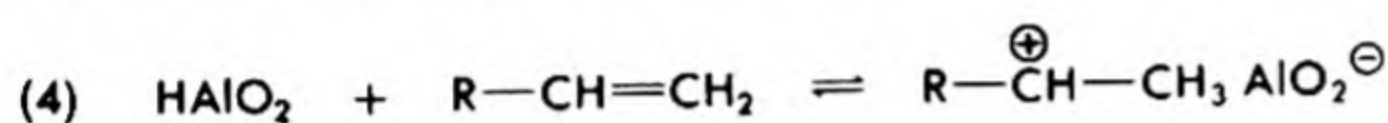
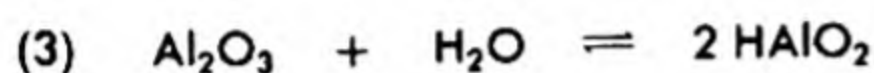


Fig. 44-1. Fluid Catalytic Cracking Plant.

gradually becomes coated with coke, and the regenerator, in which the coke is burned off. The heat of the regeneration process is utilized to heat the reactants to the cracking temperature. Fluid processes have been developed for other heterogeneous catalytic reactions as well.

Catalytic cracking is a carbonium ion process. Many complex changes occur, including chain breaking, isomerization of chains, isomerization of rings, multiple bond migration, and even some polymerization (the reverse of cracking). Only a few of the major changes which lead to the cracked product are represented in the following equations.

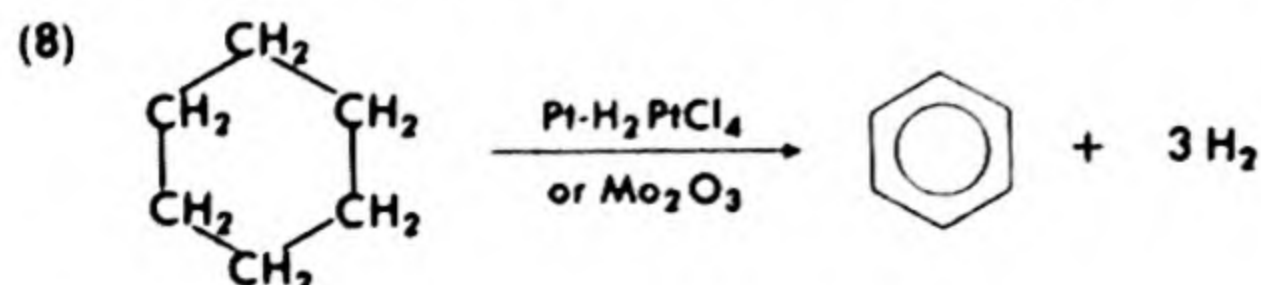


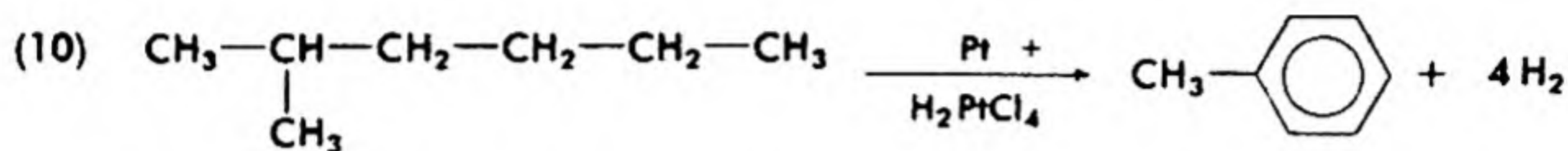
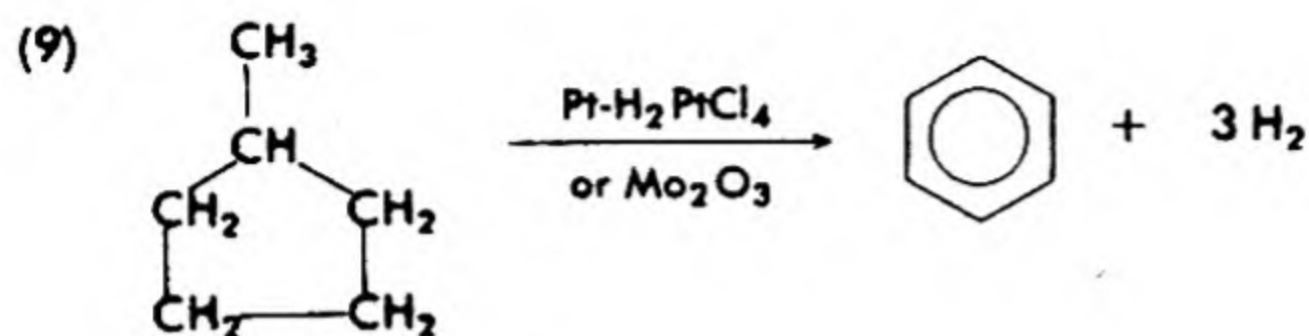
(2) *Reforming*. Reforming is a process involving cyclization and dehydrogenation. The several reforming processes in operation differ in the extent to which chain branching, olefin formation, cyclization, and aromatization occur.

Reforming over chromia on alumina converts cycloparaffins to aromatic compounds. Isomerization of cyclopentane derivatives to cyclohexane derivatives also occurs over molybdena or cobalt molybdate on alumina. There is little conversion of open chain compounds to arenes (cyclo-dehydrogenation).

Reforming over platinum-based catalysts effects both cyclodehydrogenation and aromatization. Cracking and isomerization of alkanes also occur to some extent.

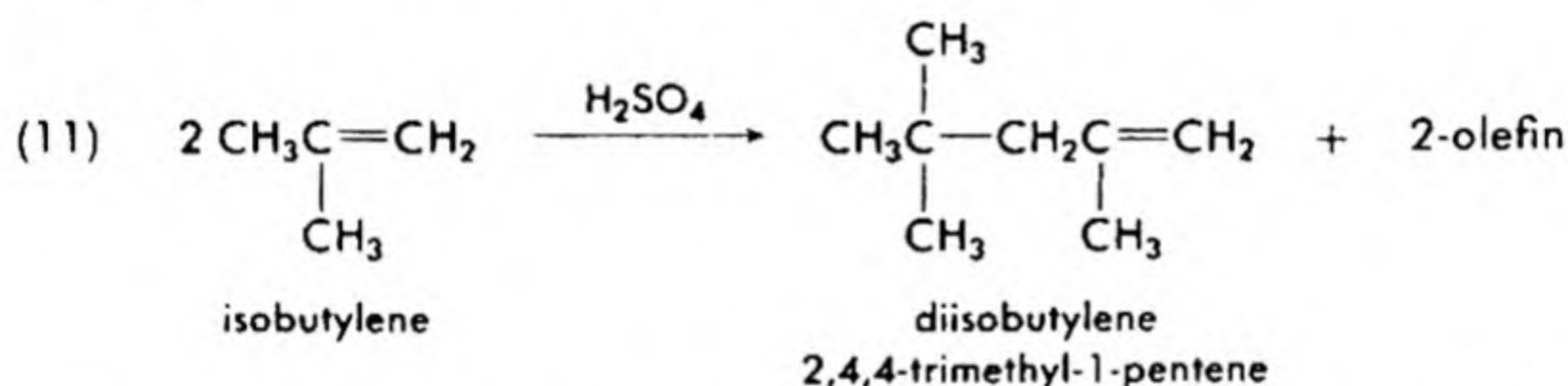
Little is known of the mechanism of reforming. Since platinum is a hydrogenation-dehydrogenation catalyst, reforming with this catalyst probably occurs by a reversal of the mechanism of hydrogenation (§27-1B). Some of the typical overall reactions are given in eqs. (8) to (10).





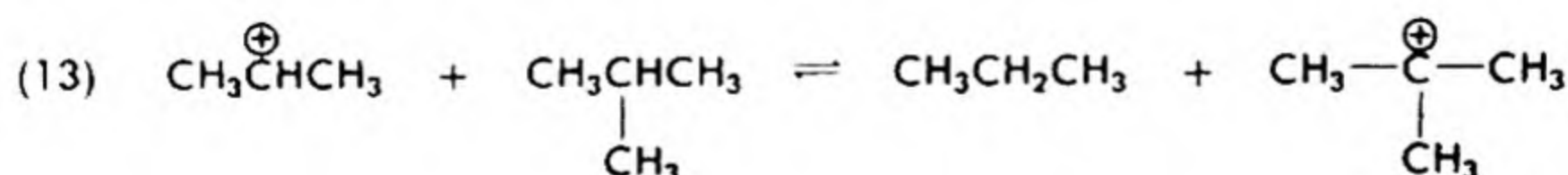
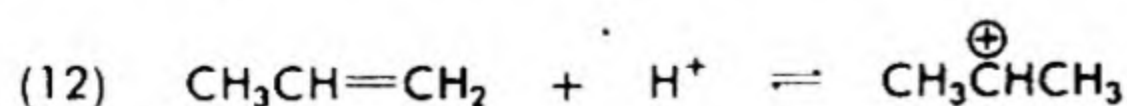
Reforming can be made to produce mainly aromatic compounds. Benzene, toluene, and some xylenes are prepared for the synthetic organic chemicals industries in this way.

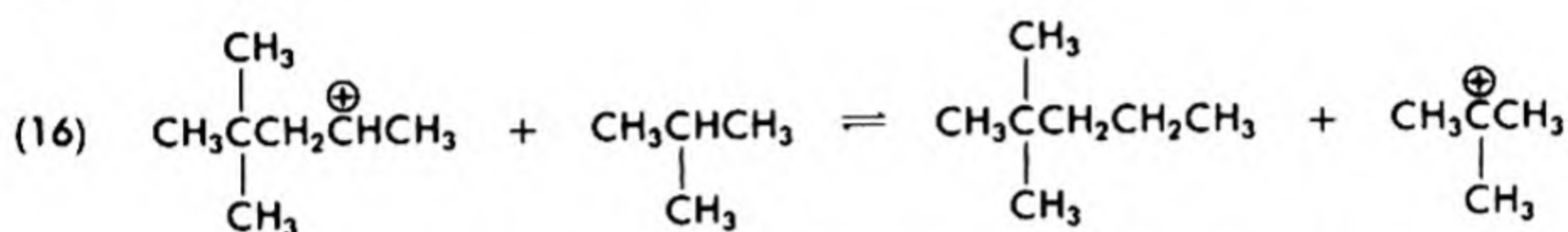
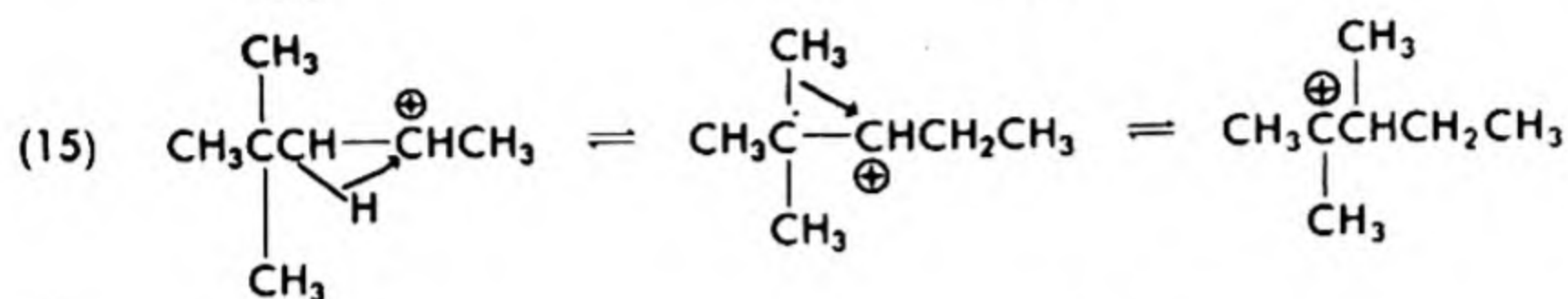
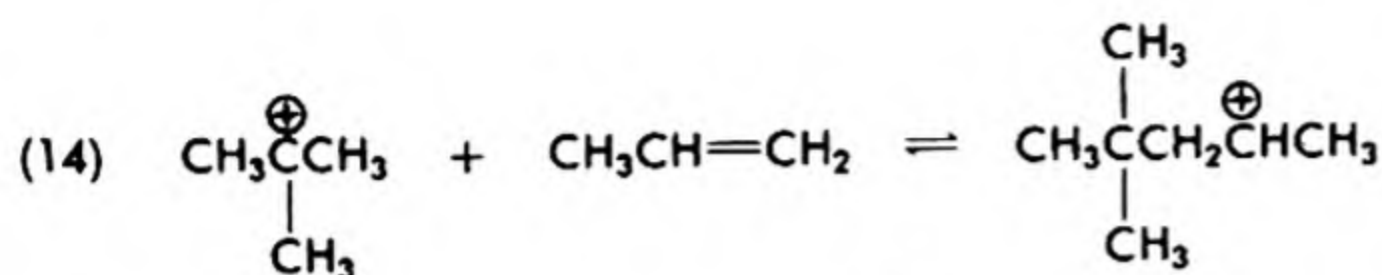
(3) *Polymerization.* Polymerization may be utilized by the refiner to synthesize hydrocarbons which boil in the gasoline range (20–200°) from the large amounts of olefin gases obtained in cracking. It is desirable for the polymerization to proceed only a few steps, so as to obtain six to ten carbon atoms per molecule. High polymer formation decreases the yield. Sulfuric acid or phosphoric acid catalysts are utilized for polymerization. The order of reactivity of olefins in polymerization is isobutylene > 2-butene > 1-butene > propylene > ethylene. The dimerization of isobutylene is illustrated in outline (11).



(4) *Alkylation.* Alkylation differs from polymerization in that one of the reagent molecules is saturated. Under the conditions of the usual alkylation reaction, the processes that occur are addition of alkane to alkene, addition of alkene to alkene, isomerization, and hydrogen exchange. Some cracking also occurs.

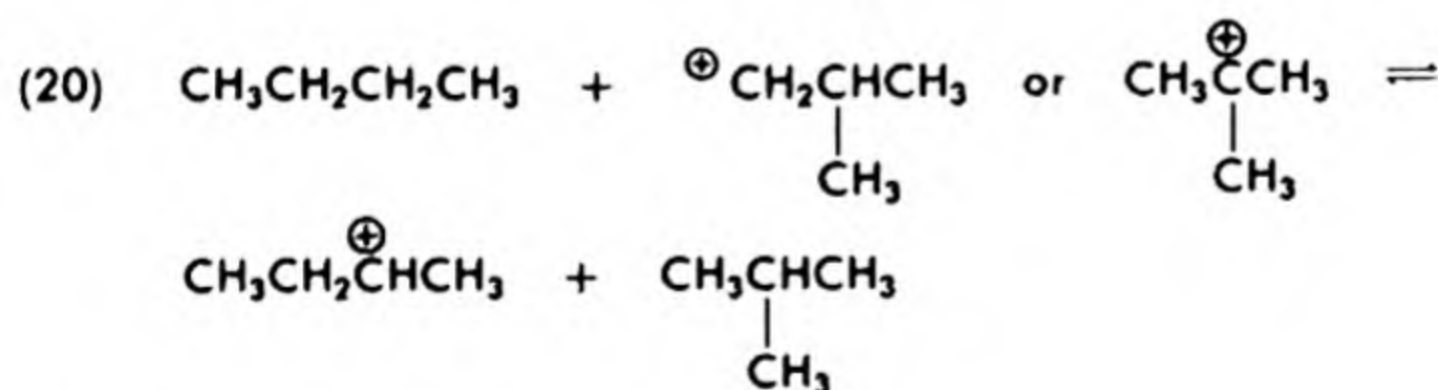
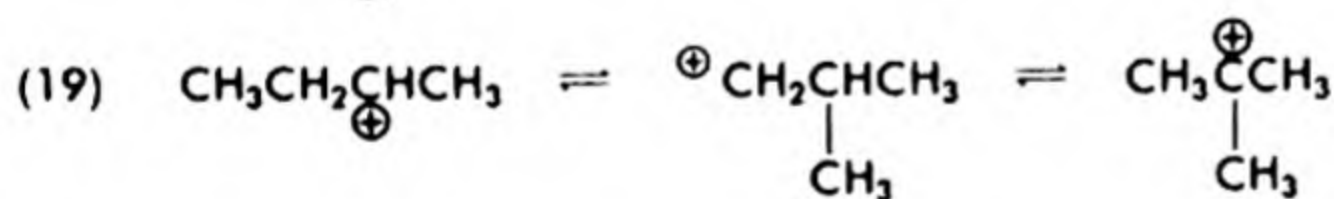
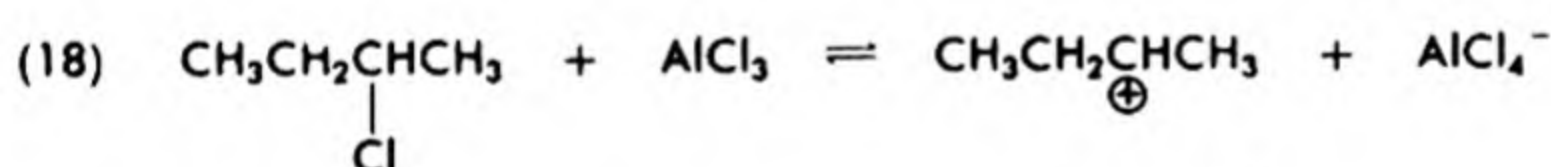
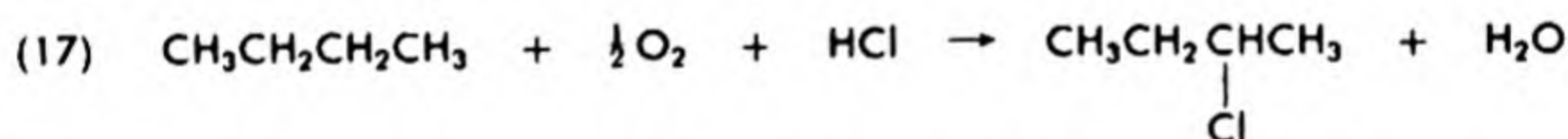
The most widely used alkylation catalysts are sulfuric acid and hydrofluoric acid. Carbonium ion intermediates are proposed. The mechanism for alkylation of isobutane by propylene is given in eqs. (12) to (16). Only a few representative steps of the ion-chain mechanism are shown.





(5) *Isomerization.* Isomerization occurs during many of the other refining processes, as has been pointed out. However, to provide ample isobutane for alkylation requires a separate isomerization process. An equilibrium is established between butane and isobutane in the presence of a suitable acid catalyst, such as anhydrous aluminum chloride with hydrogen chloride.

Again a carbonium ion mechanism is proposed (eqs. 19 and 20). A little air must be present to initiate the reaction by providing a carbonium ion source (eqs. 17 and 18), or alternatively, an alkyl halide or olefin may be added in trace amounts.



44-2 PETROLEUM PRODUCTS

Gasoline is the main petroleum refinery product. It accounts for about 46% of the volume of crude oil. This product controls the economic position of the petroleum industry.

Diesel fuel and heating fuel comprise the second major market for petroleum products. These materials come from the kerosene and light gas oil fractions of petroleum.

Liquefiable petroleum gases, consisting largely of propylene, propane, butane, and ethylene are a third major product. The saturated materials are used for portable heating and cooking units and all are sources of petroleum chemicals. Much of the refinery gas output is utilized to heat retorts and stills in the refinery.

Lubricants, consisting of oils and greases, form a fourth major product. Greases are oils to which metal soaps have been added as jelling agents.

A number of specialty products, such as wax, petrolatum and petroleum solvents make up the balance of the refinery output.

SUPPLEMENTARY READINGS

"Additives for Petroleum Products" (Symposium), *Ind. Eng. Chem.* **41**, 886-962 (1949).

Nelson, W. L., *Petroleum Refinery Engineering*, 4th Ed., McGraw-Hill, New York, 1958.

Progress in Petroleum Technology, American Chemical Society, Washington, D. C., 1951, pp. 3-159, 210-220, 235-286, 334-371.

Sell, G., *The Petroleum Industry*, Oxford, New York, 1963, pp. 1-17, 86-129, 245-255.

QUESTIONS AND PROBLEMS

1. Write equations for reactions which typify the following processes.

a. catalytic cracking	d. alkylation
b. reforming	e. isomerization
c. desulfurization	f. polymerization

2. State which compound in each pair below would be expected to have the higher octane number and why.

a. <i>n</i> -pentane, <i>n</i> -hexane	d. 2-hexene, 3-hexene
b. 2,4-dimethylhexane, 2-methylheptane	e. 3-methylhexane, methylcyclohexane
c. 2,2,4-trimethylpentane, 2,3,3-trimethylpentane	f. cyclohexane, benzene
	g. toluene, xylene

45

Silicon Organic Compounds and Fluorocarbons

45-1 SPECIAL NATURE OF SILICON ORGANICS

The mountains of the world are mute testimony to the durability of mineral matter, most of it silicious. On the other hand, the realm of carbon chemistry provides the utmost flexibility, variety, and selectivity. The marriage of these two elements was expected to provide something original. In this respect, the discoverers of silicones, Frederick S. Kipping and his co-workers, were not disappointed.

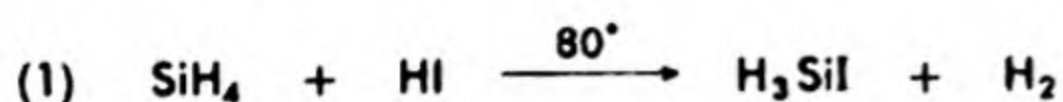
The union of small hydrocarbon groups with silicon-oxygen chains results in products with high thermal stability, together with some unique properties, such as relative independence of certain physical properties to temperate differences. For example, silicone oils change little in viscosity between temperatures from -50° to 500° .

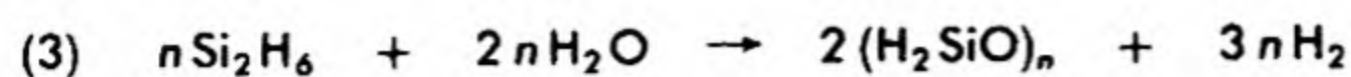
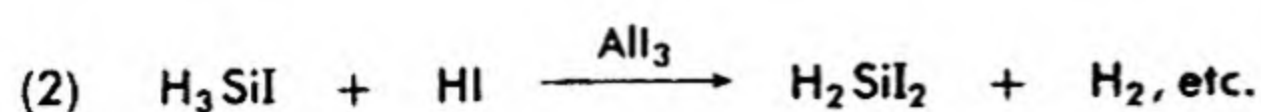
Chemical inertness and lack of affinity for other materials are other characteristics of silicones. Silicone oils do not swell rubber, nor are silicone rubbers swelled by ordinary oils and greases.

45-2 SIMPLE ORGANOSILICON COMPOUNDS

A. Silicanes

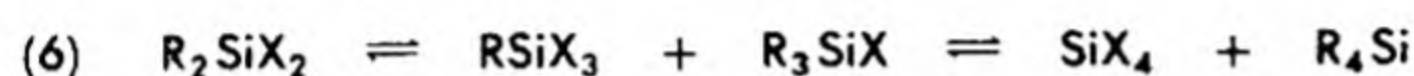
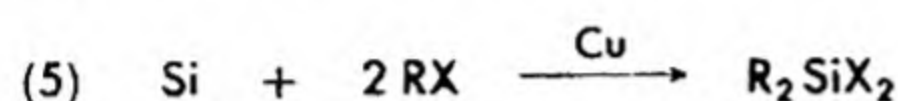
Not all silicon compounds share the stability and inertness of those in which silicon atoms are connected by oxygen atoms. The silicon-hydrogen bond is a weak and highly reactive one. The silicon-silicon bond also lacks the stability of the carbon-carbon bond. Consequently, strictly silicon analogs of hydrocarbons and their derivatives are few and reactive. Replacement of one or more hydrogen atoms by hydrocarbon groups does little to increase stability as long as two or more silicon atoms remain connected together, or as long as hydrogen atoms remain on silicon atoms. Thus, silane, or silicane, SiH_4 , and its homologs react rapidly with many reagents, in contrast to the behavior of alkanes.





B. Alkyl Chlorosilanes

The silicon organic compounds of primary interest as raw materials are alkylated silicon halides. These materials are produced mainly by two methods. One is the treatment of silicon tetrahalides with Grignard reagents; the other, direct reaction of elementary silicon with alkyl halides in the presence of copper. By either method, mixtures of all possible mono and polyalkyl derivatives are formed.



The ability of alkylsilicon halides to interchange halogen atoms and alkyl groups provides a means of modifying the ratio of products by introducing silicon tetrahalide or tetraalkylsilane and heating the mixture with a catalyst. The products can be separated by distillation, since the boiling points differ appreciably in most cases (Tables 45-1 and 45-2).

TABLE 45-1. Boiling Points of Alkylchlorosilanes

Formula	Name	Boiling Point
SiCl_4	Silicon tetrachloride	57.6°
CH_3SiCl_3	Methyltrichlorosilane	64.6
$(\text{CH}_3)_2\text{SiCl}_2$	Dimethyldichlorosilane	69.4
$(\text{CH}_3)_3\text{SiCl}$	Trimethylchlorosilane	59
$(\text{CH}_3)_4\text{Si}$	Tetramethylsilane	26.6
$\text{C}_2\text{H}_5\text{SiCl}_3$	Ethyltrichlorosilane	99-101
$(\text{C}_2\text{H}_5)_2\text{SiCl}_2$	Diethyldichlorosilane	130-131
$(\text{C}_2\text{H}_5)_3\text{SiCl}$	Triethylchlorosilane	143.5
$(\text{C}_2\text{H}_5)_4\text{Si}$	Tetraethylsilane	154.7

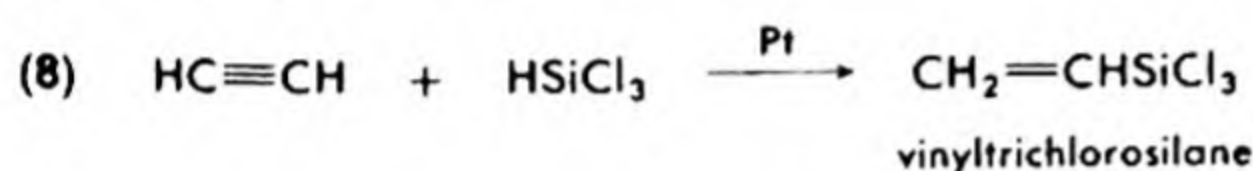
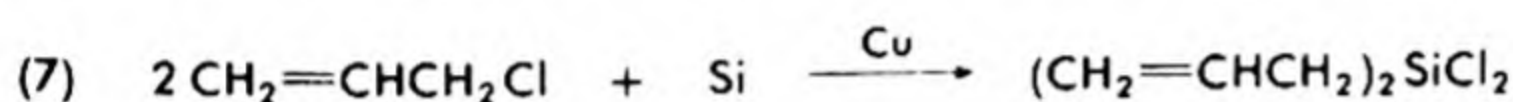
TABLE 45-2. Physical Properties of Phenylchlorosilanes

Formula	Melting Point	Boiling Point
$\text{C}_6\text{H}_5\text{SiCl}_3$	88-89°	197°
$(\text{C}_6\text{H}_5)_2\text{SiCl}_2$	188	305
$(\text{C}_6\text{H}_5)_3\text{SiCl}$	88-89	378
$(\text{C}_6\text{H}_5)_4\text{Si}$	234	360

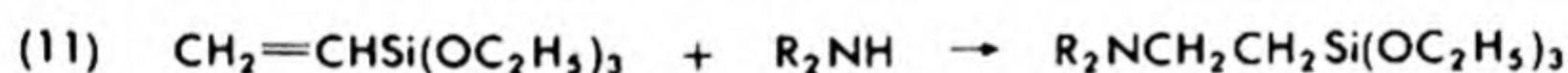
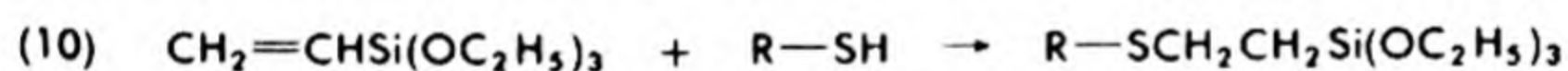
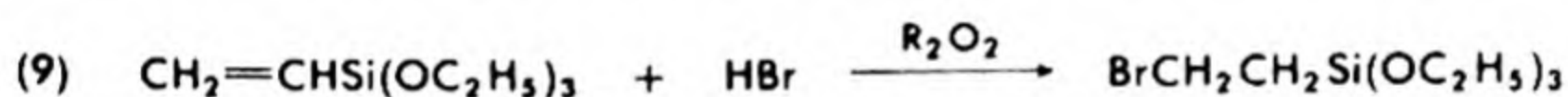
C. Carbon-Functional Silicon Organics

The very inertness of hydrocarbon groups attached to silicon atoms that is attractive in silicones is a hindrance to introduction of groups by substitution. Other methods had to be devised. It is not suitable in most cases to have the functional group already present on the carbon atom when the group is joined to the silicon atom, since the silicon halides and halogenosilanes that are starting materials or intermediates react readily with many functional groups.

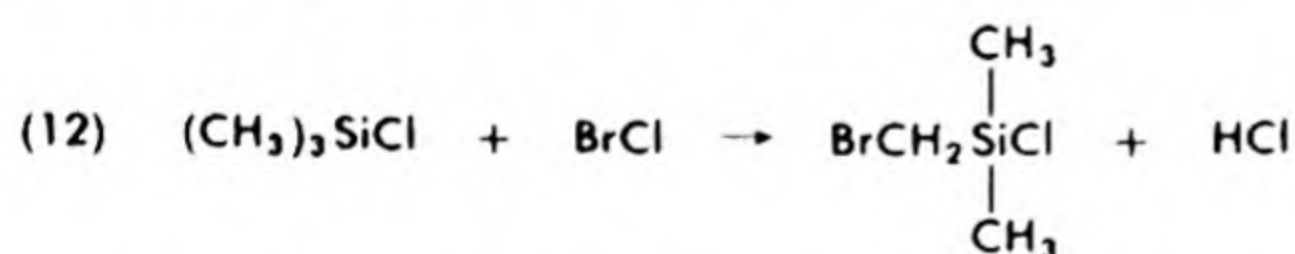
Double bonds can be introduced into organosilicon compounds by using unsaturated halides in the reaction with silicon or by treatment of partly chlorinated silanes with acetylene (eqs. 7-8). The vinyl silanes show the addition reactions of double bonds connected to electron-withdrawing atoms. This is just the reverse of the conjugative effect noted with halogen



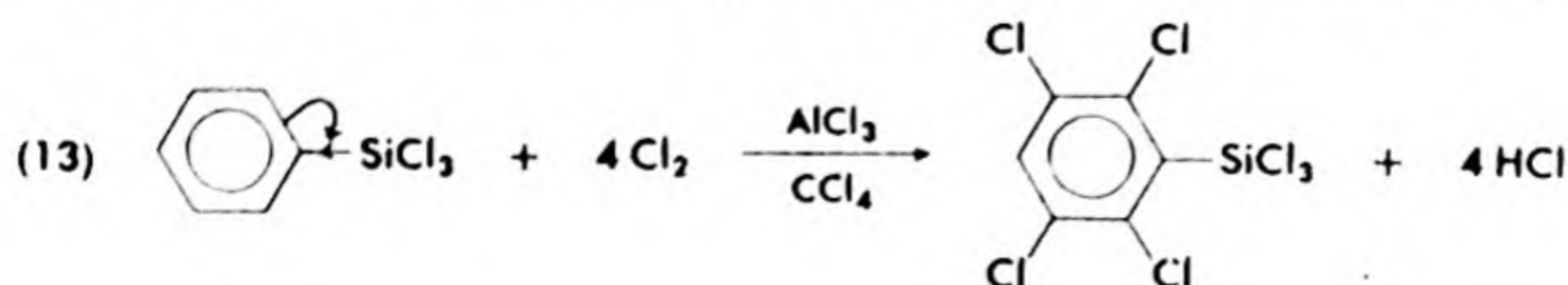
atoms. The silicon atom, which can expand its valence level to as many as six pairs of electrons, withdraws electrons conjugatively, releases them inductively. Orientation of groups going into the double bond is indicated in eqs. (9) through (11). Other vinylsilicon compounds behave similarly.



Halogenation can be accomplished by substitution, but special conditions are required. Bromination of methylchlorosilanes, for example, is best accomplished using bromine chloride.

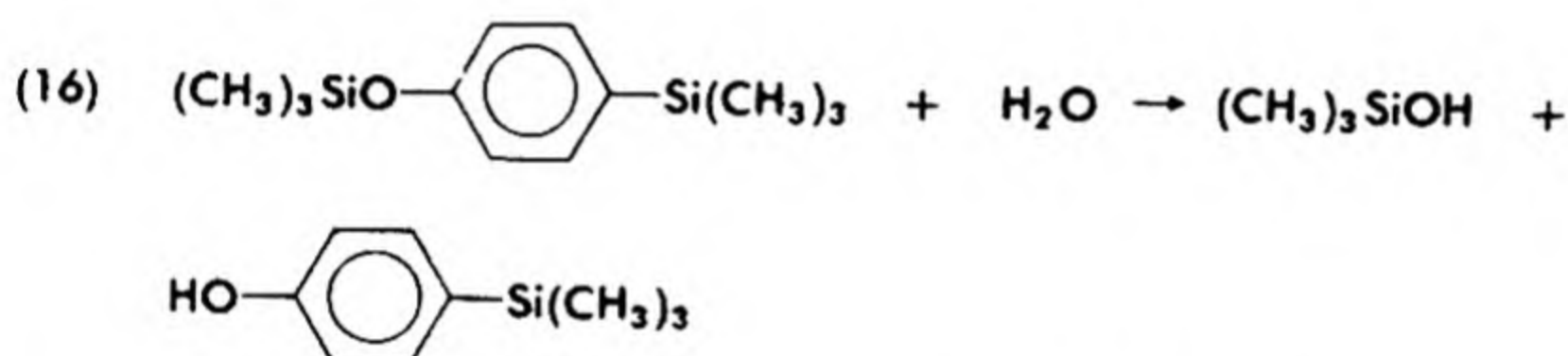
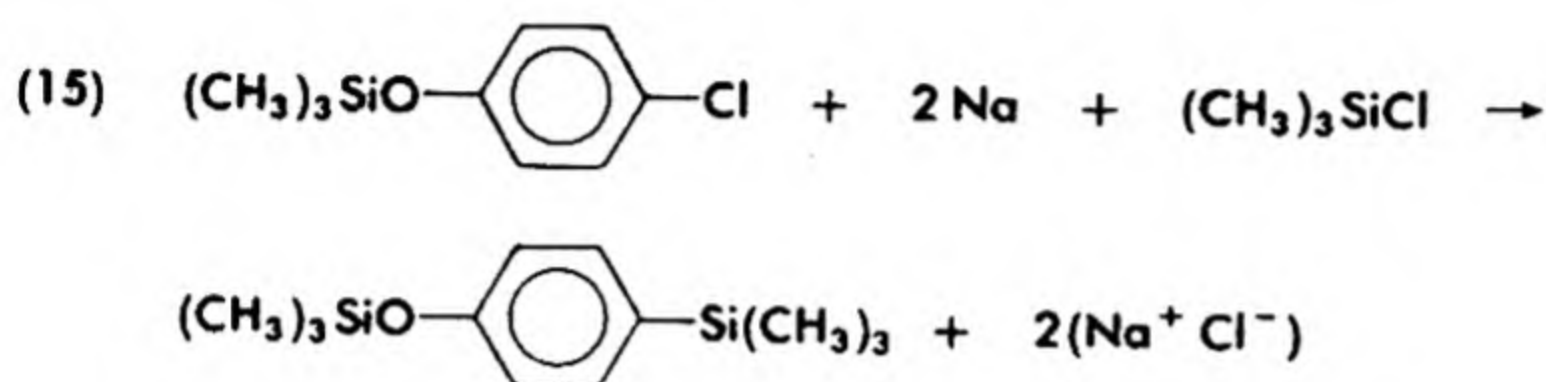


An example of the unusual electronic influence of the silicon atom is its effect on chlorination in the benzene ring. The *para* position is de-

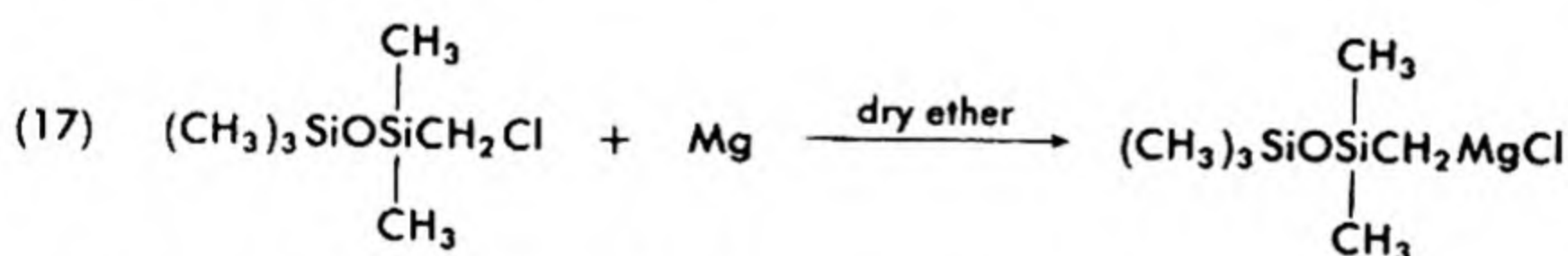


activated by the conjugative electron withdrawal, but the *ortho* and *meta* positions are activated by the inductive electron release.

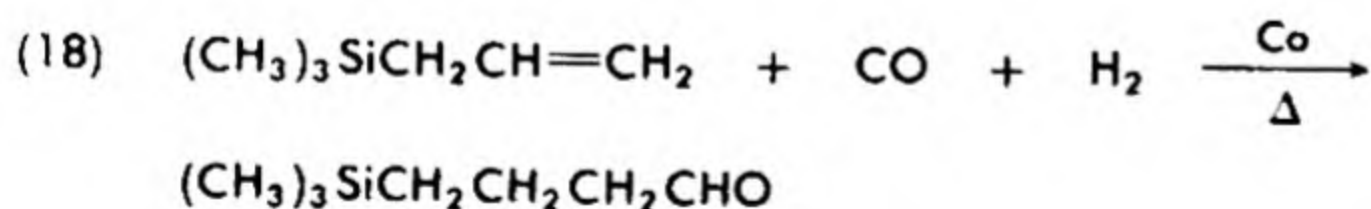
A modified Wurtz-Fittig synthesis (eq. 15) can be used to introduce certain carbon-functional radicals into silanes. The example given shows use of another silane derivative as a protective group.



Grignard reagents can be prepared from chloromethylsilicon compounds; this opens the way for the introduction of a wide variety of functional groups.



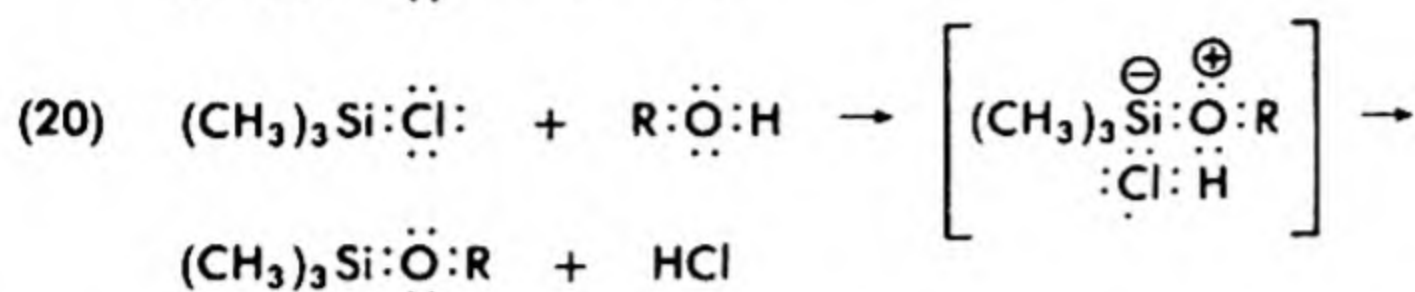
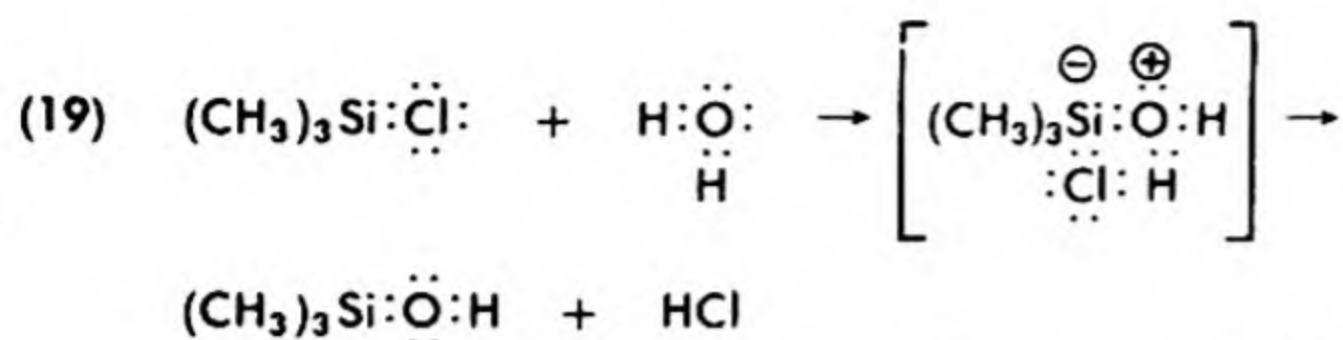
The Oxo process has also been used to prepare aldehydes from allyl silanes.



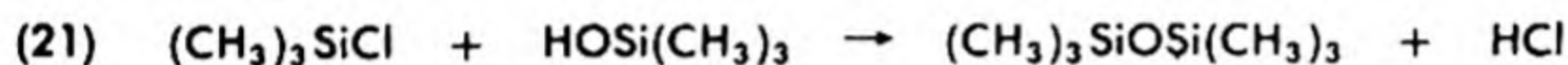
D. Reactions of Silicon Functions

The utility of halogenosilanes is a result of the high reactivity of the silicon-halogen bond. This is due to the ability of the silicon atom to expand its valence level (eq. 19).

Halogenosilanes are readily hydrolyzed to the hydroxy compounds and alcoholized to silicate esters.



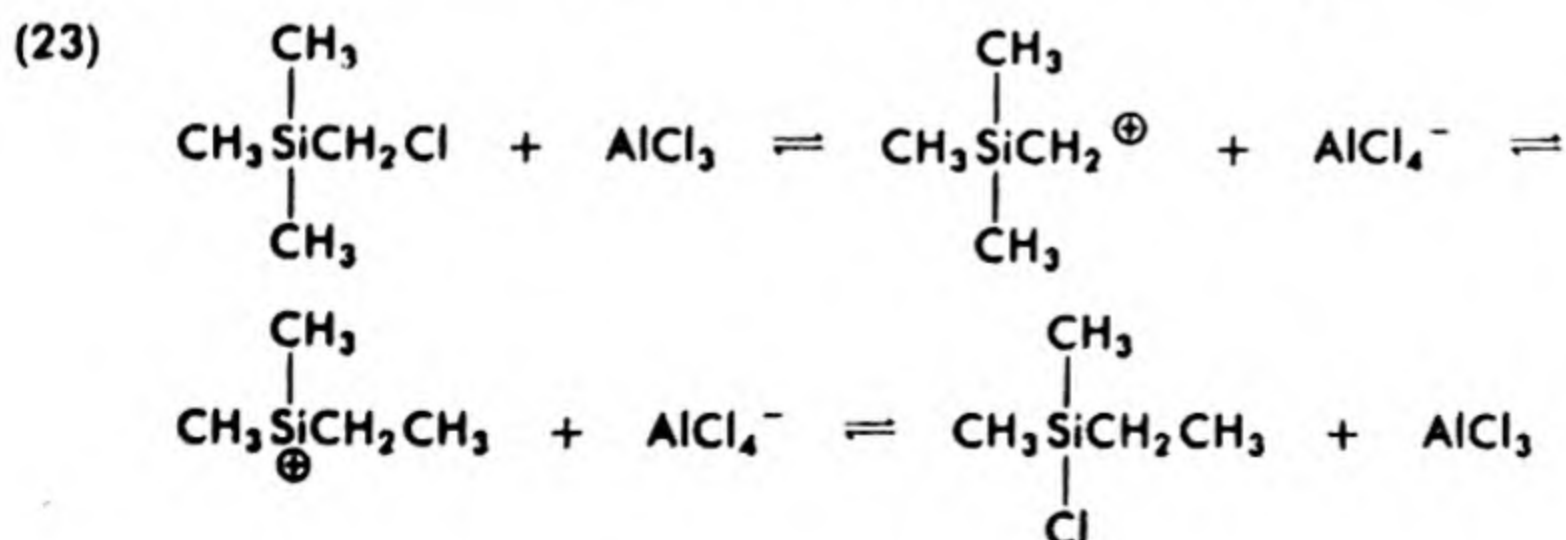
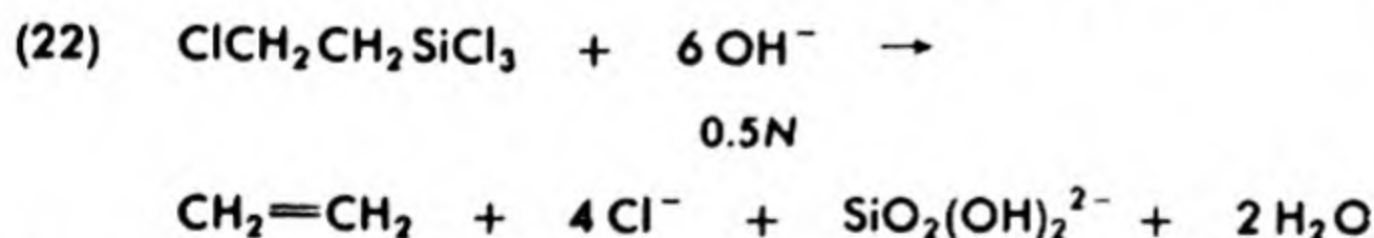
Unlike the corresponding carbon compounds, silicon di- and trihydroxides have no tendency to dehydrate to ketone-like or carboxylic-like compounds. Instead, the *ortho* acids and esters are formed. Silicon does not readily form multiple bonds. Silicon-oxygen-silicon bonds (analogous to the Williamson synthesis) are easily formed.

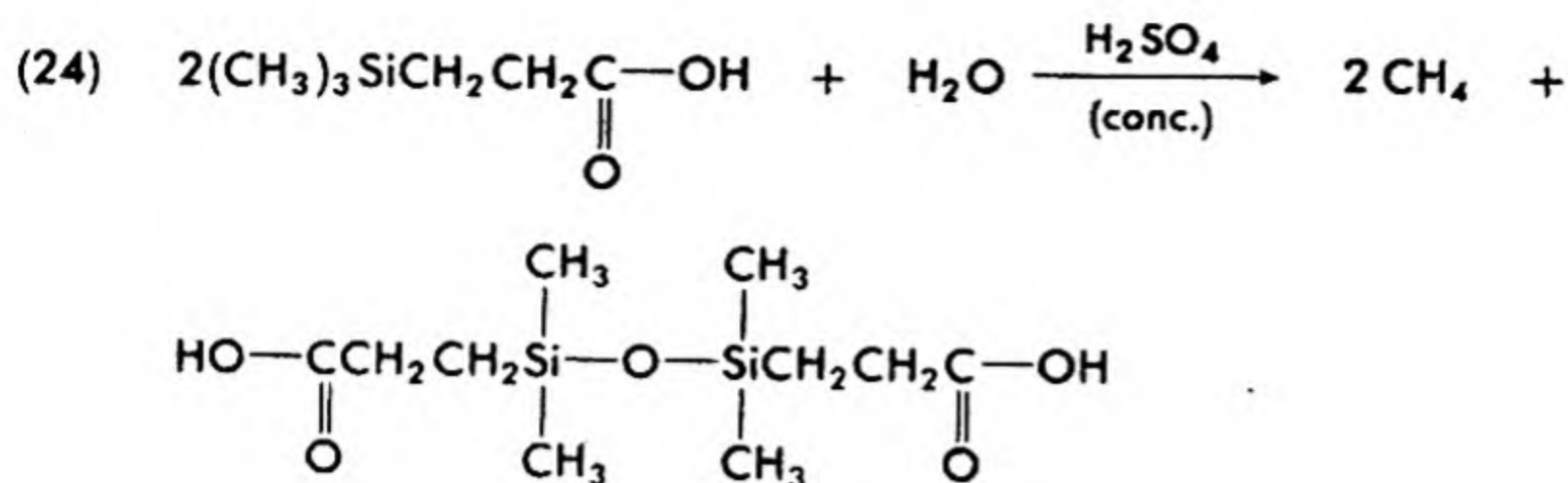


This type of silicon-oxygen-silicon linking is an outstanding characteristic of silicon. It is responsible for the large number of silicon compounds in the same way that the ability of carbon atoms to form chains is responsible for the vast number of carbon compounds. Reactions such as that indicated in eq. (21) are responsible for the formation of silicones. Silicon-oxygen-silicon linking can be promoted by using the minimum amount of water in hydrolyzing chlorosilanes. The reaction can be avoided only by using a large excess of water during the hydrolysis.

Silicate esters are readily hydrolyzed. Treatment with mild alkali or even water cleaves the esters to give silicon hydroxides and oxides (see eq. 16).

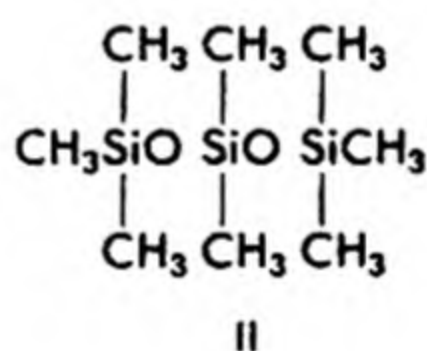
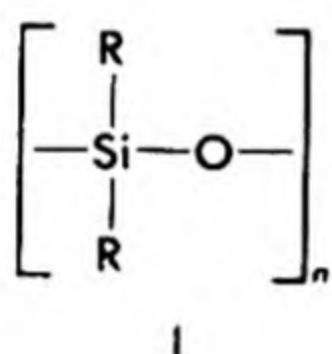
Some silicon-carbon bonds are readily cleaved. Dehydrohalogenation of a chloroethyl group is accompanied by such cleavages. Aluminum chloride causes rearrangements in chlorosilanes similar to those in hydrocarbon halides. Soluble silanes can be cleaved by heating with strong acid.





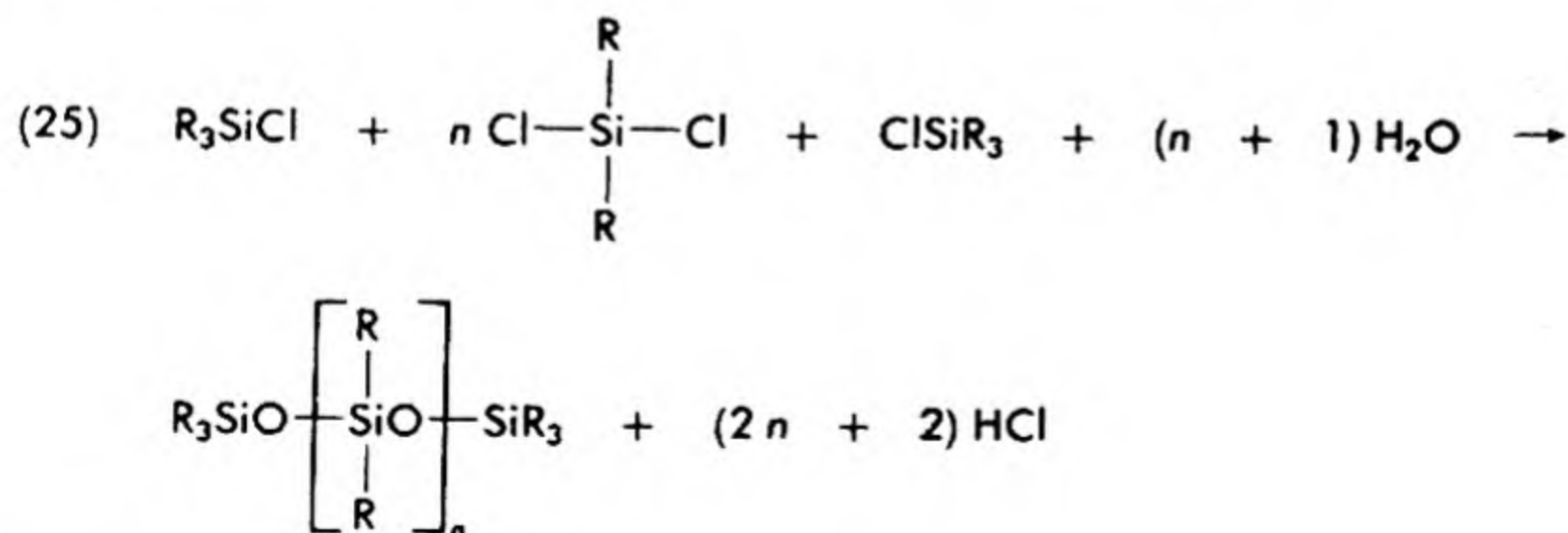
45-3 SILICONES

The term silicone is applied to organosilicon compounds of the composition R_2SiO . However, it is apparent that silicones do not in any way resemble ketones; their structures and properties are those of polyoxysilylenes, I. The term *siloxane* has been accepted as the official designation of this type of compound. The usual numerical prefixes indicate the number of silicon atoms present, as in octamethyltrisiloxane, II. Silicones are prepared from appropriate mixtures of alkylchlorosilanes by hydrolysis.



A. Silicone Oils and Waxes

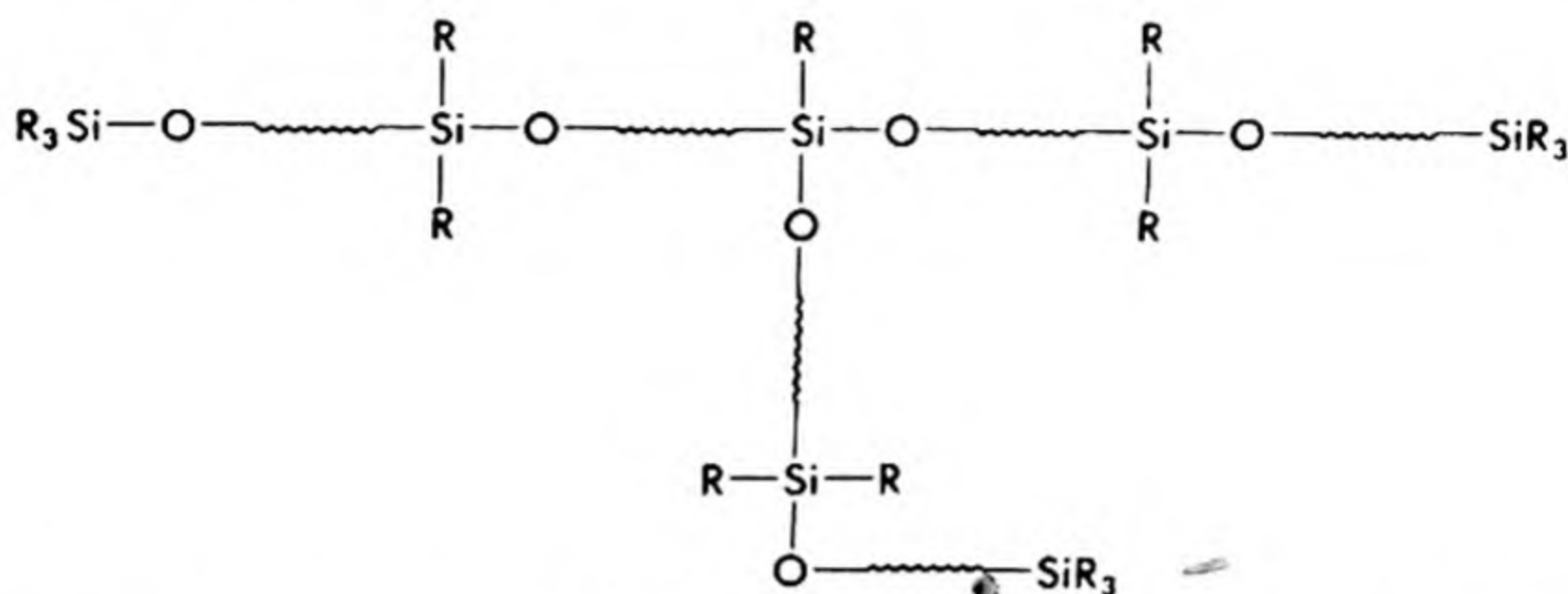
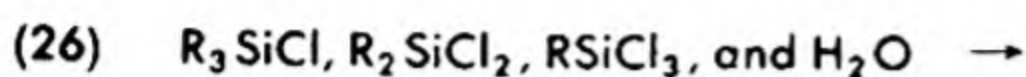
Treatment of mixtures of dialkyldichlorosilanes and trialkylchlorosilanes with water gives linear siloxanes. Depending on their molecular weights, these compounds are oils or waxy solids. The average molecular weight of the mixture can be controlled by the proportion of the components.



B. Silicone Rubbers and Resins

Inclusion of some alkyltrichlorosilane in the halide mixture provides for the formation of branched siloxanes. If the proportion of alkyltrichlorosilane is higher, not only branching but some cross linking can occur,

leading to a network polymer. When the degree of cross linking is low, an elastic material, a *silicone rubber*, is produced. If the cross linking is extensive, dimensionally stable resins are produced.



Even more extensive cross linking is achieved by adding traces of silicon tetrachloride to the mixture. However, large amounts of this compound in the polymerization mixture must be avoided because local regions of silica can be formed, which are hard, brittle, and unworkable.

45-4 USES OF SILICON ORGANIC MATERIALS

Although still quite expensive on a weight basis, silicon organic materials have become major items of commerce. Three of the largest areas of use are waterproofing, electrical insulating, and mold releasing.

Methyl and ethyl chlorosilanes are volatile compounds. As was pointed out, they readily form silicate esters. Thus, these compounds can be used to vapor treat cloth, paper, and wood, as well as ceramics (cement, porcelain, etc.) to make the surface so water-repellant that large drops of water can be made to cover treated cotton marquisette (an open-weave net used for curtains) without passing through the open mesh.

Electrical equipment with silicone rubbers and resins as insulation, and silicone oils as transformer oils, can be operated at high temperatures. This makes possible designs of much smaller size for the same power rating.

The use of talc, soaps, fats, and the like to prevent molded objects from sticking to the molds is at best messy and involves frequent cleaning of charred release agents. Silicone mold-release agents, which are not degraded by heat and are very little absorbed by the tires, baked goods, foam mattresses, etc., which are made in the molds, last a long time and seldom need to be cleaned off the mold. Furthermore, the molded products are smoother and cleaner than those made with the older release agents.

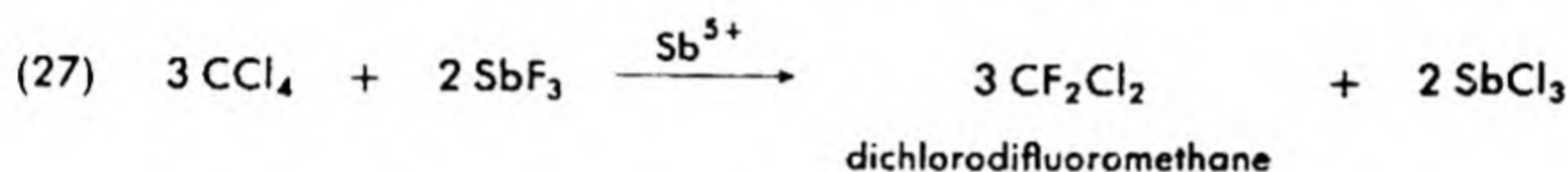
Silicone oils are used as nonflammable hydraulic fluids. Silicone greases are useful lubricants for some purposes. Other specialty uses for silicones are polishing and surface protective coating, defoaming, and high-low temperature gasket sealing.

45-5 FLUOROCARBONS

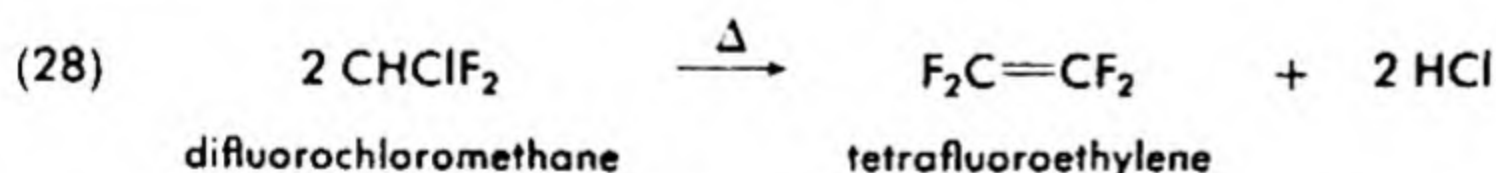
Fluorocarbons, hydrocarbon analogs in which all hydrogen atoms are replaced by fluorine atoms, also often show chemical inertness and many other properties similar to those of silicones. Fluorocarbons are chemically inert to all substances but molten alkali metals.

In general, fluorocarbons are made by substitution in hydrocarbons using electrolytically produced fluorine or perchloryl fluoride, FCIO_3 . Special apparatus is required. A field of chemistry is growing around these compounds. Properties of some functional fluorocarbon derivatives are analogous to, others quite different from, those of the related hydrocarbon derivatives.

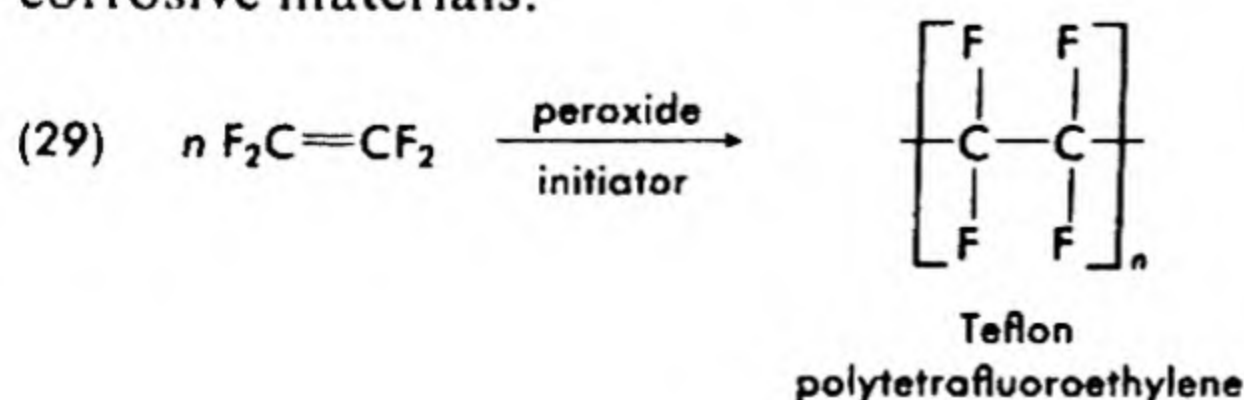
Certain fluorinated methane and ethane derivatives which also contain other halogens are prepared by displacement reactions. For example, dichlorodifluoromethane (Freon-12) is prepared from carbon tetrachloride (eq. 27). This compound, which boils at -30° , is used in large



amounts as a refrigerant in household refrigerators and as a propellant for aerosol bombs. Difluorochloromethane is prepared in similar fashion from chloroform and antimony trifluoride in the presence of pentavalent antimony. Pyrolysis of this compound leads to tetrafluoroethylene (eq. 28).



Polymerization of tetrafluoroethylene gives Teflon (eq. 29). (Polymerization is discussed in §46-1.) Teflon polytetrafluoroethylene is a long-chain fluoroparaffin which is both thermally stable and inert to reagents. This polymer also has a very low coefficient of friction. These properties make it very useful for gaskets and bearings in equipment for handling corrosive materials.



SUPPLEMENTARY READINGS

- Eaborn, C., *Organosilicon Compounds*, Butterworths, London, 1960.
- George, P. D., M. Prober, and J. R. Elliott, "Carbon-Functional Silicones," *Chem. Rev.* **56**, 1065-1219 (1956).
- Hudlicky, M., *Chemistry of Organic Fluorine Compounds*, Macmillan, New York, 1962.
- Lovelace, A. M., D. A. Rausch, and W. Postelnek, *Aliphatic Fluorine Compounds*, Reinhold, New York, 1958.
- McGregor, R. R., *Silicones and Their Uses*, McGraw-Hill, New York, 1954.
- Pavlath, A. E., and A. J. Leffler, *Aromatic Fluorine Compounds*, Reinhold, New York, 1962.
- Sommer, L. H., *Stereochemistry, Mechanism and Silicon*, McGraw-Hill, New York, 1965.
- Wilk, I. J., "Comparative Organic Chemistry: Carbon and Silicon," *J. Chem. Educ.*, **34**, 463-465 (1957).

QUESTIONS AND PROBLEMS

- What special properties make siloxanes attractive for certain uses? How do other organosilicon compounds compare with siloxanes in respect to these properties?
- Compare the reactivities of the following bonds.

a. C—C, C—Si, and Si—Si	d. C—O and Si—O
b. C—H and Si—H	e. C—H, C—Cl, and C—F
c. C—Cl and Si—Cl	
- Show how the following compounds can be prepared from the suggested starting materials and inorganic reagents, including silicon and silicon halides. Use structural formulas for organic compounds. Indicate reagents and necessary special conditions.
 - Hexaethyldisiloxane from ethylene
 - Diethylaminoethyltriethoxysilane from acetylene
 - 3-Trimethylsilyl-1-propanol from methanol, diazomethane, and ethylene
 - A continuous chain silicone oil of average composition corresponding to polymethyleicosasiloxane from methanol
 - A branched silicone of average composition corresponding to a polyethyl-tricontasiloxane with two branches and a phenyl group at each branch from ethanol and benzene
 - A network silicone polymer with an average of five diethylsiloxy units between cross-links from ethanol
 - Trifluoroacetic acid from carbon tetrachloride



Polymerization and Polymers

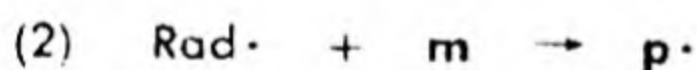
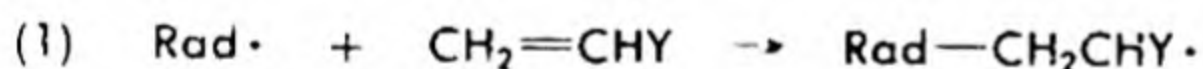
46-1 POLYMERIZATION

The combination of unsaturated molecules to form a polymer is termed *addition polymerization*. Reactions of polyfunctional alcohols, anhydrides, amines, and isocyanates, for example, to form polymeric ethers, esters, amides, or urethanes are called *condensation polymerization*. These latter polymerizations involve ordinary solvolysis. Although for some purposes dimers, trimers, and other low oligomers are desired, in general only high polymers containing many monomer units have properties which make them useful as fibers, films, elastomers, or resins.

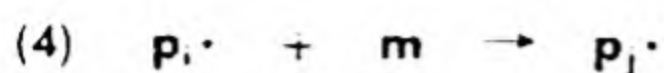
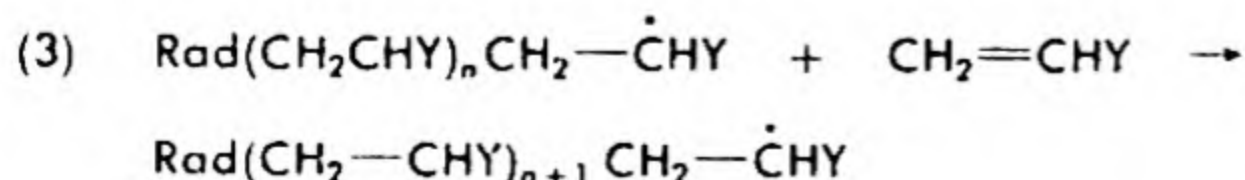
A. Mechanisms of Addition Polymerization

(1) *Free Radical Processes.* It was shown (§26-4D) that addition of a free radical to any olefinic double bond produces a new free radical, and that this radical may also add to an olefinic bond, provided the energy and kinetic relationships are favorable.

The formation of the initiating radical by thermal or photochemical decomposition of an unstable compound, such as a peroxide, together with the addition of the radical to an olefinic bond, is termed *chain initiation* (eq. 1 or 2).

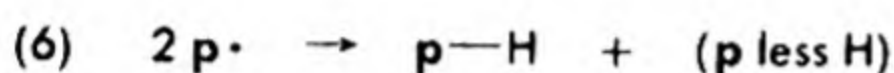
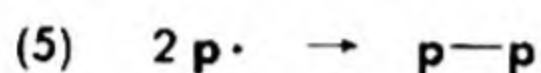


Next, if the alkyl radical attacks the monomer more readily than the radical source, or if the concentration of the radical source is very low, *chain propagation* occurs (eq. 3 or 4). In the propagation portion of the process, successive monomer units add to the growing (radical) end of the polymer molecule.

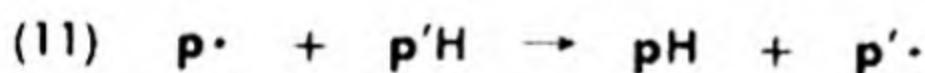
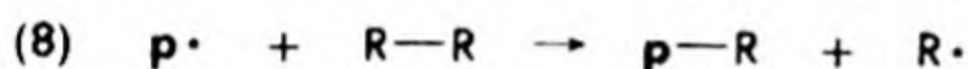


In the conventionalized eqs. (2) and (4), $\text{Rad}\cdot$ represents the initiating radical, m the olefinic monomer, and $\text{p}\cdot$ the growing polymer chain. Subscripts i and j denote differing chain lengths. Since there is virtually no difference in the reactivity of growing polymer chains at different lengths, the studies of rates of polymerization do not distinguish any of the propagation stages.

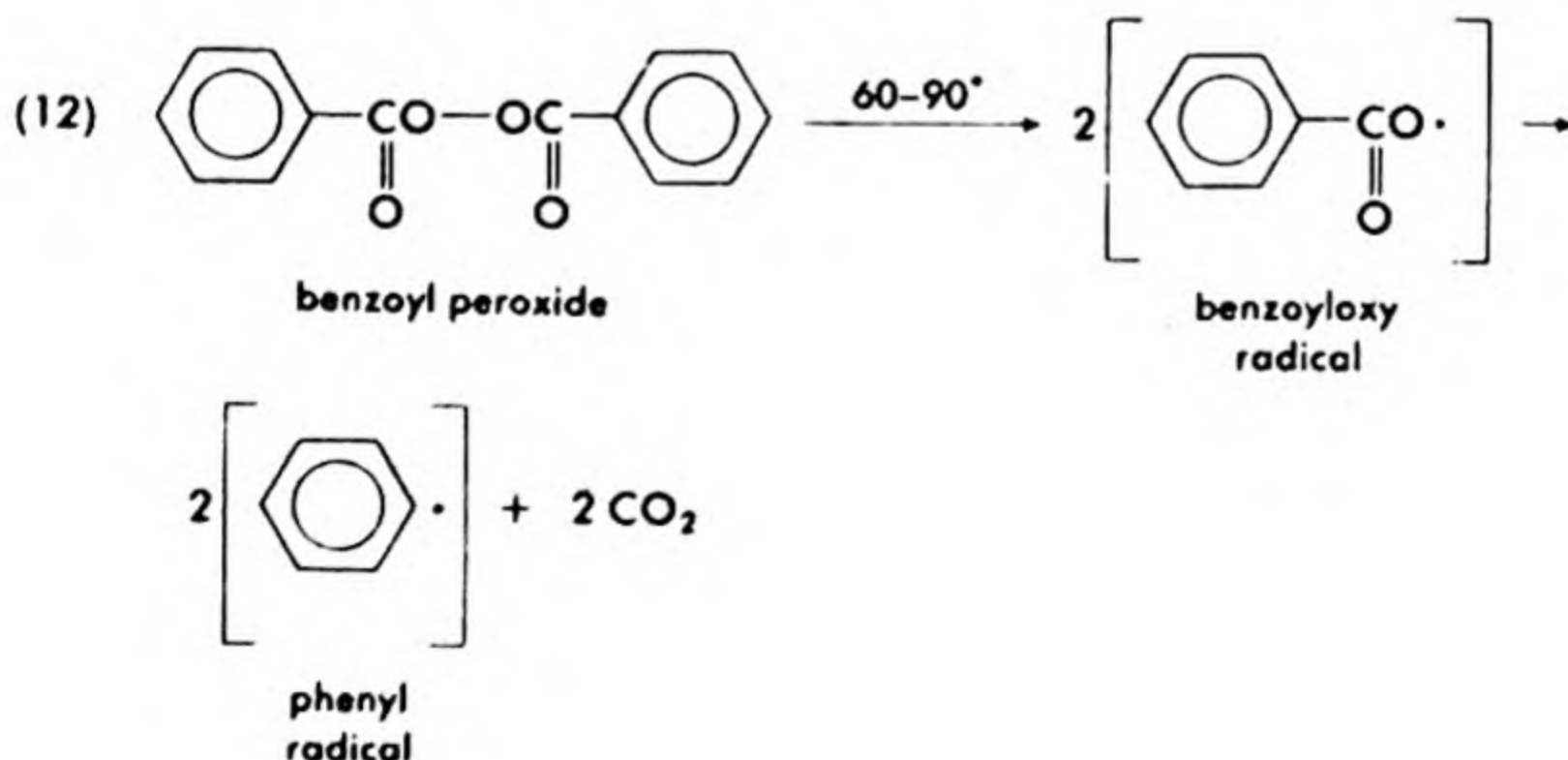
The third stage is *chain termination*. This can be accomplished by any of three processes. The polymer radical can couple with another polymer radical (eq. 5), disproportionate (eq. 6), or combine with a radical from the radical source (eq. 7) (see §26-4A).



In addition to these steps a process called *chain transfer* can occur. One polymer radical abstracts an atom from a normal molecule to form a new radical. Some chain-transfer steps (eqs. 8, 9, and 10) result in moderation of molecular weights, but have no effect on polymer yield. Others (eq. 11) result in branching, since the radical, $\text{p}'\cdot$, has a much higher probability of being formed in the interior of the chain than at the end.



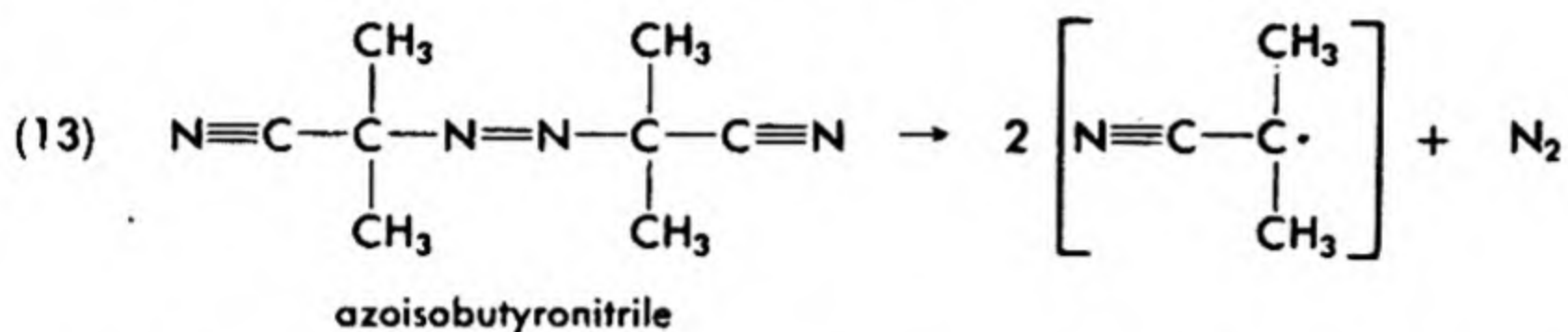
In these equations, $\text{R}-\text{R}$ represents the initiating radical source, sH a solvent molecule, and $\text{s}\cdot$ a free radical produced from the solvent. Each of the radicals produced in eqs. (8) through (11) can in turn initiate a new



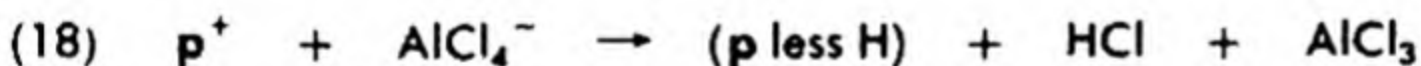
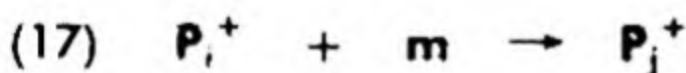
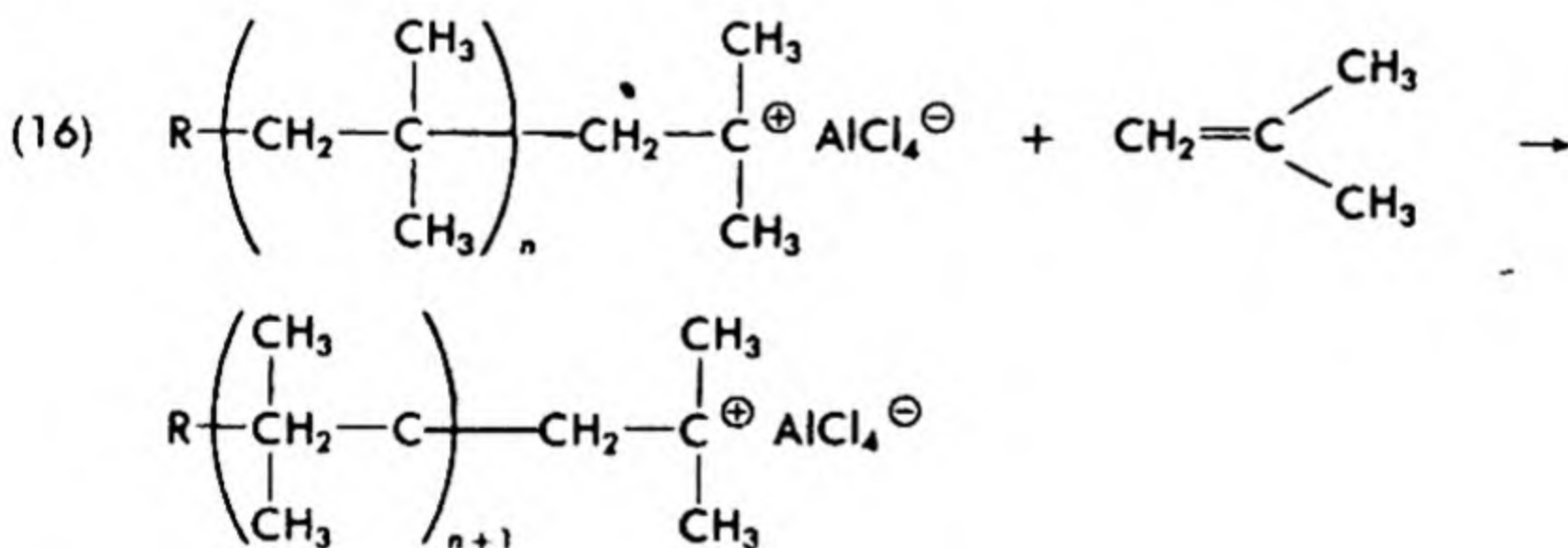
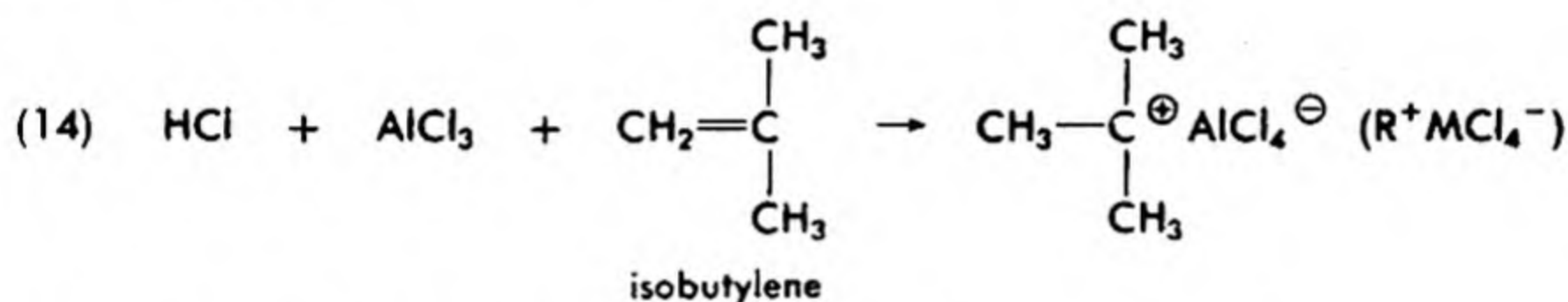
polymer chain, provided the radical is active. If the radical produced in eq. (9) is not active, the substance sH is an inhibitor, that is, it stops the polymerization.

Several types of radical sources are used for polymerizations. Organic peroxides cleave smoothly upon moderate heating.

More recently developed radical sources include azonitriles. Alkali metals may also serve as radical sources.



(2) *Carbonium Ion Processes.* A second mechanism of polymerization involves carbonium ions. This mechanism resembles the radical mechanism in many respects; it also has steps of initiation, propagation, and termination.

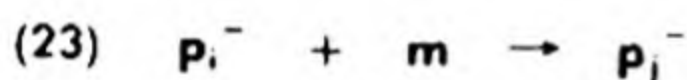
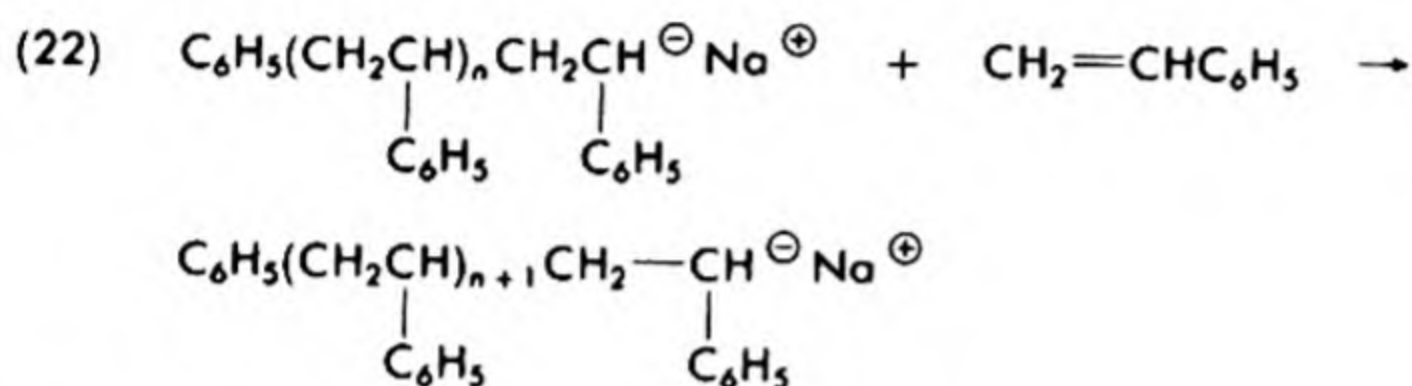
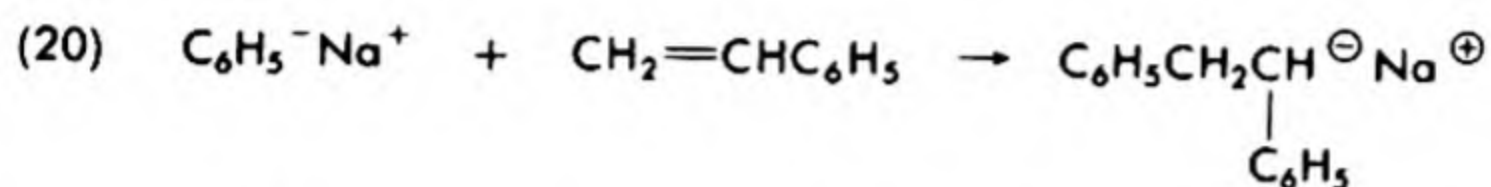


Symbols in eqs. (14) through (19) have significances similar to those in eqs. (2) through (11). The AlCl_4^- in eq. (18) is the anion from which the hydrogen ion originally separated. In eq. (19), s is a solvent molecule and Hs^+ is a solvated hydrogen ion.

Initiation of carbonium ion polymerization requires a strong acid. Mix-

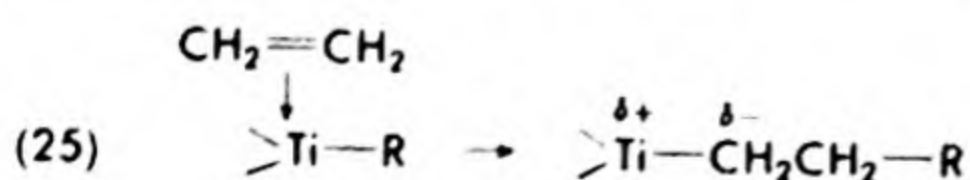
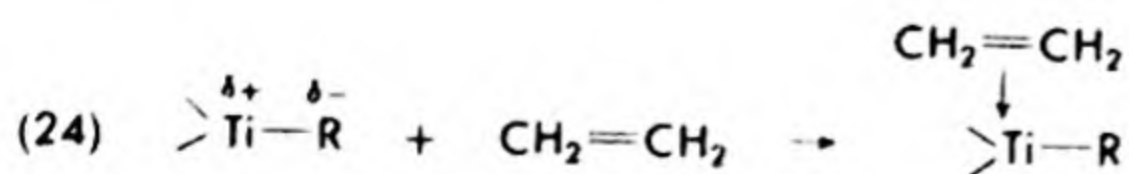
tures of AlCl_3 or BF_3 with HCl or HF have been used. Acid-catalyzed polymerization is most successful with isobutylene.

(3) *Carbanion Processes.* A number of activated olefins or dienes will polymerize in the presence of strong bases or alkali metal alkyls. For example, styrene can be polymerized with phenylsodium according to the following steps:



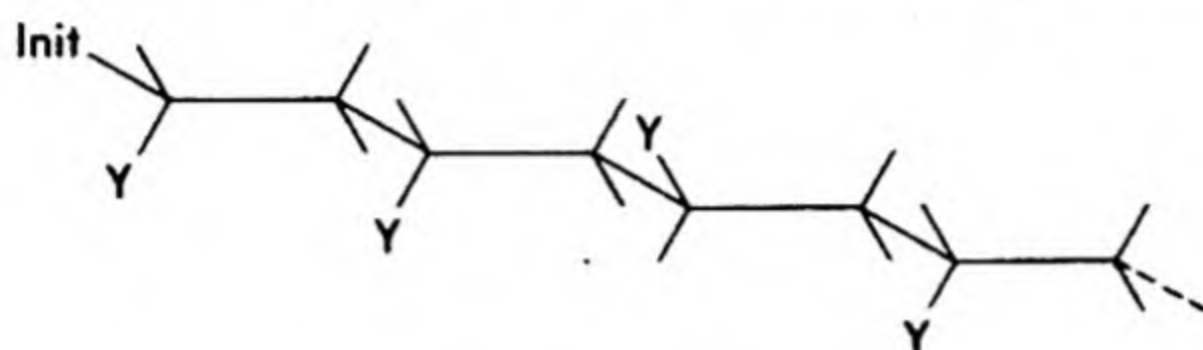
Symbols in eqs. (21) and (23) have significances similar to previous symbols. Note that the polymerization ends when the monomer is completely consumed and the polymerization is initiated again when fresh monomer is added. A polymer of this sort is therefore called a *living polymer*. When a species containing active hydrogen is added (water, alcohol, etc.) the organometallic end is transformed to carbon-hydrogen bond. No further polymerization will then occur.

(4) *Coordination Polymerization.* When olefins such as ethylene, propylene, or butadiene are passed over certain reduced metal oxides or treated with mixtures of aluminum alkyls and titanium or vanadium chlorides, useful polymers result. Polymerization of ethylene gives an unbranched product, the polymerization of propylene gives a stereoregular polymer (see §46-1A(5)) while butadiene may give *cis*-1,4-, *trans*-1,4- or stereoregular 1,2-polybutadiene, depending on the catalyst used. The polymerization is believed to involve initial coordination of olefin on a catalyst complex (eq. 24), followed by insertion into the metallo-organic bond (eq. 25).

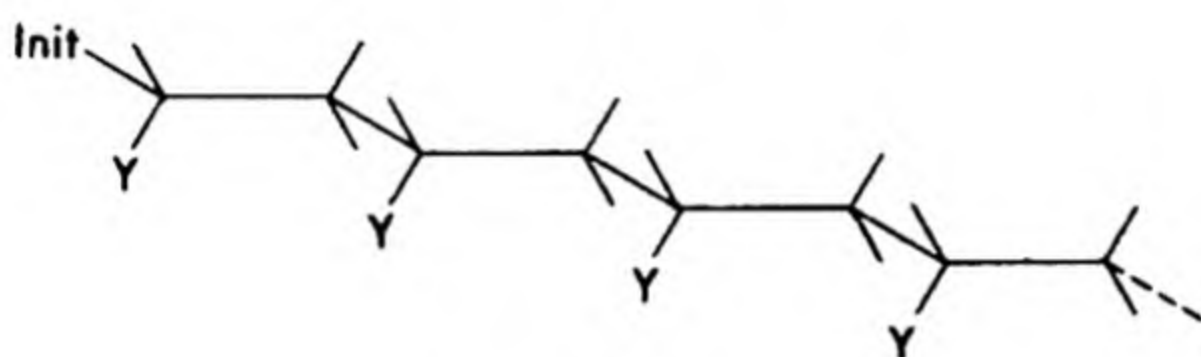


Karl Ziegler (Mulheim) and Giulio Natta (Milan) shared the Nobel prize in chemistry in 1963 for their work on coordination polymerization.

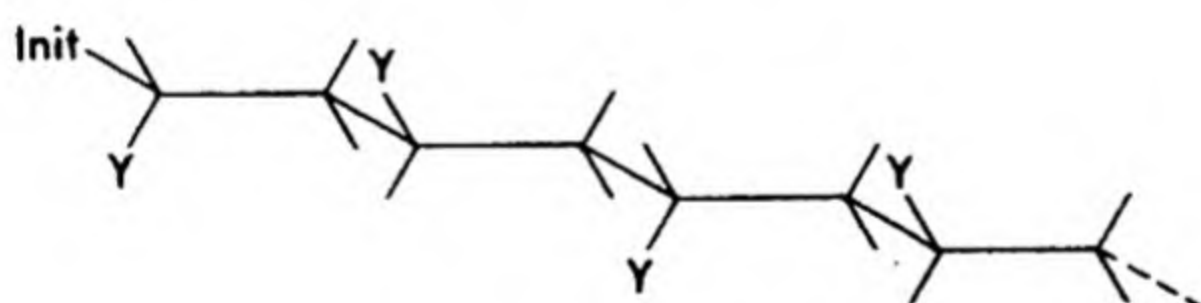
(5) *Stereoregular Polymers.* In the polymerization of a vinyl monomer, $\text{CH}_2=\text{CHY}$, three gross stereochemical results are possible, depending upon the spatial relationships of adjacent side chains. If the polymerization is random, the polymer is termed *atactic*. If all of the side chains may be represented in parallel configurations, the polymer is called *isotactic*. A *syndiotactic* polymer has alternating side chains in opposite configurations. All three types of polymers are realizable by industrial processes.



atactic polymer



isotactic polymer



syndiotactic polymer

The three types of polymers are diastereoisomeric and therefore have different properties. Atactic polymers have lower melting points and less crystallinity than stereoregular isotactic and syndiotactic materials. This could be anticipated on the basis of their abilities to pack into solid crystals.

(6) *Chain Length in Polymers.* Once an addition polymerization chain is initiated, it continues very rapidly until terminated. A full polymer molecule may be made in a fraction of a second. In addition polymerization involving initiation and termination steps, more and more full polymer molecules are formed until the monomer or the initiator is consumed. However, in condensation polymerization, conventional reactions keep adding to the chains as long as the reaction progresses (see Fig. 46-1).

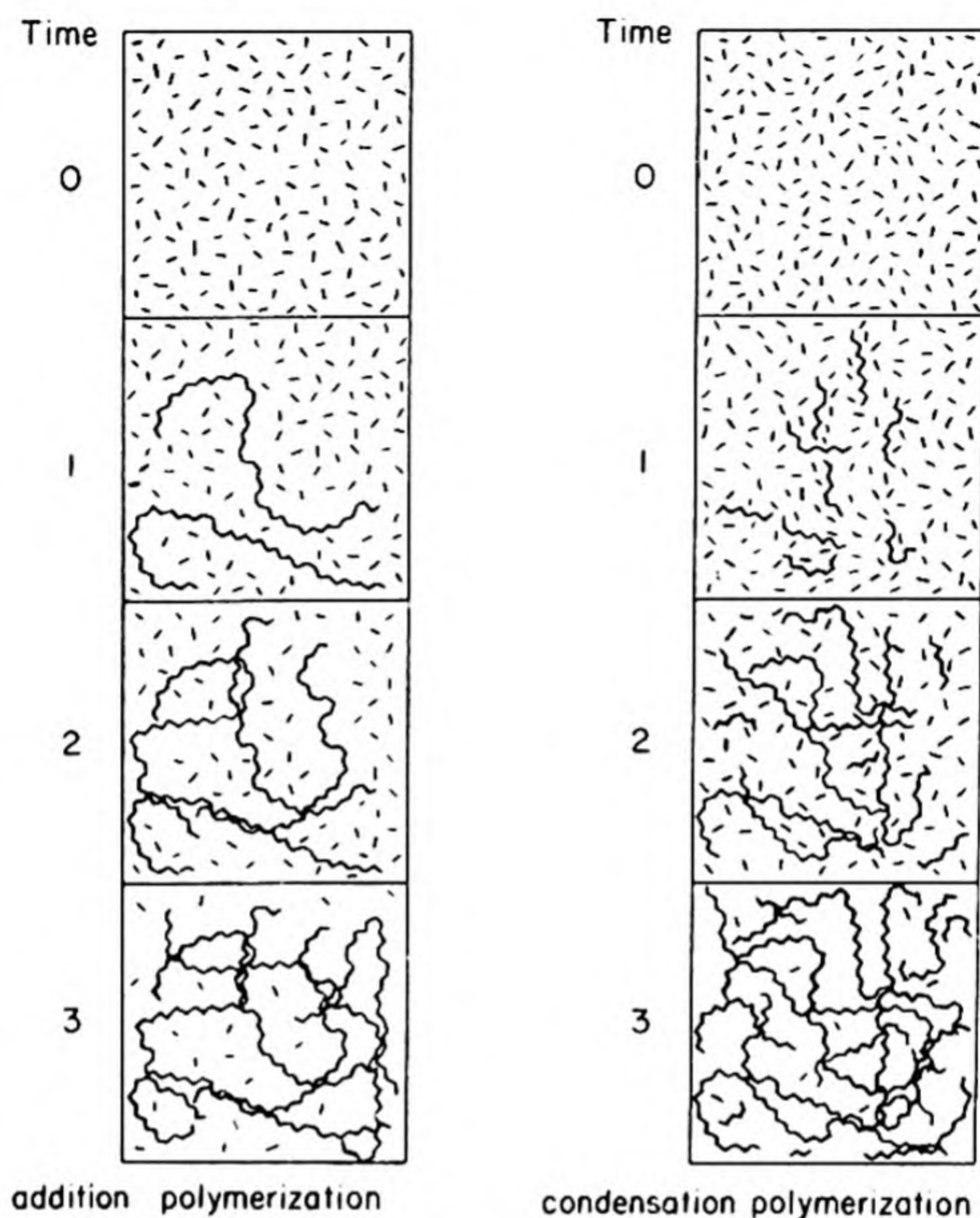


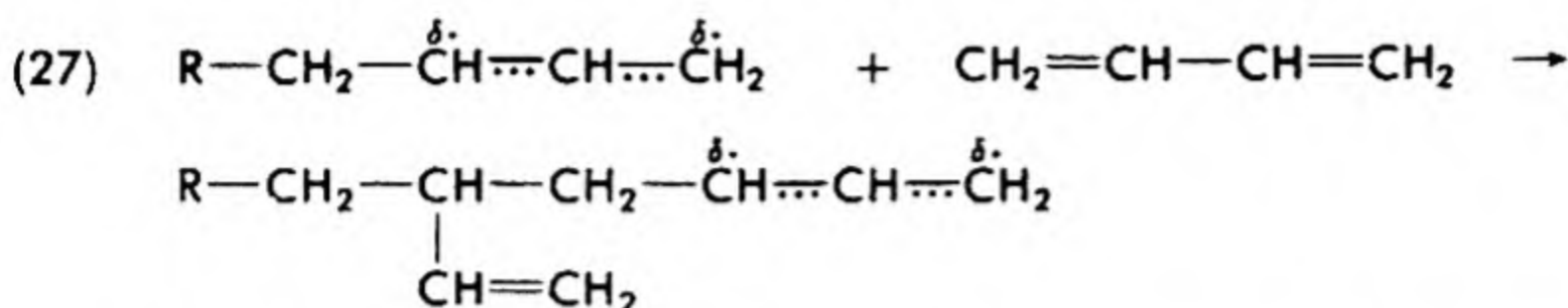
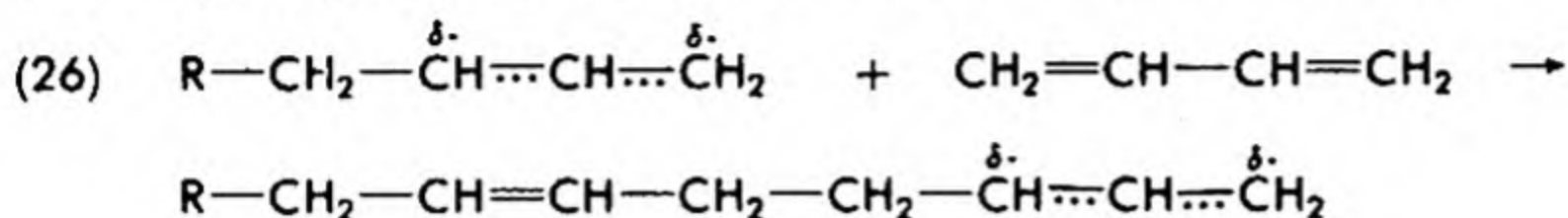
Fig. 46-1. Chain Growth in Polymerization.

Chain length in addition polymerization, therefore, depends on the ratio of the rate of chain termination to chain initiation in the absence of chain transfer agents. This, in turn, depends on the concentration of radicals present at a given time. Higher initiator concentration favors shorter chains. The average size of polymer molecules can be controlled by this factor and by temperature.

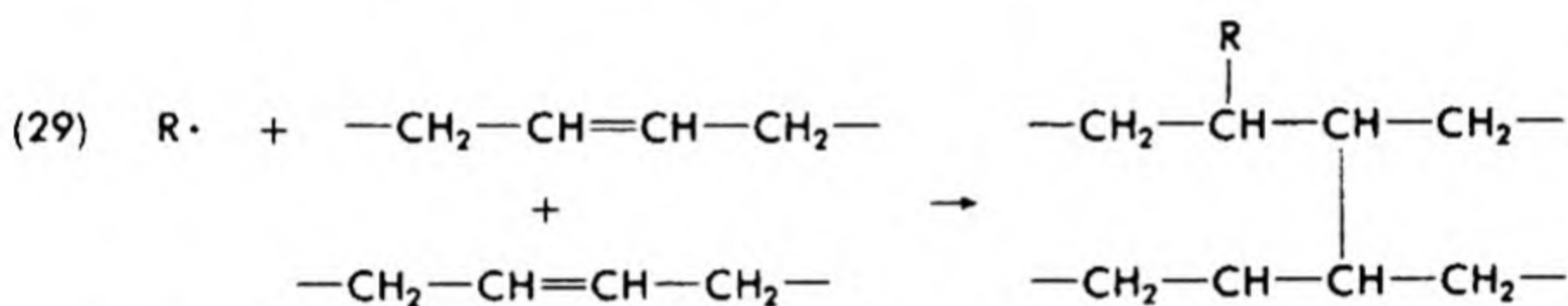
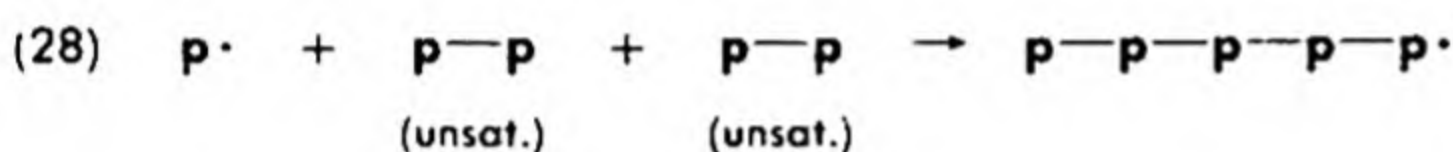
Condensation polymer chains, however, continue to grow as time progresses. Hence, control of average molecular size in condensation polymers is largely a matter of choosing the appropriate time to stop the reaction or of setting up equilibrium situations.

It is apparent that simple alkenes and their analogs give nearly saturated polymers. All of the double bonds are utilized in the addition except when chains terminate by disproportionation, in which case, one of the two chains retains a double bond. Alkadienes and their analogs, how-

ever, utilize only one of the two double bonds in forming a linear chain, whether they add 1,4 or 1,2 or a combination of these.

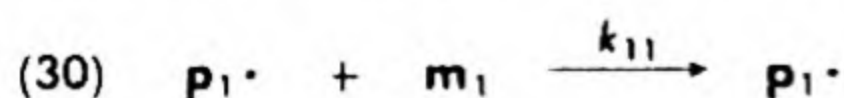


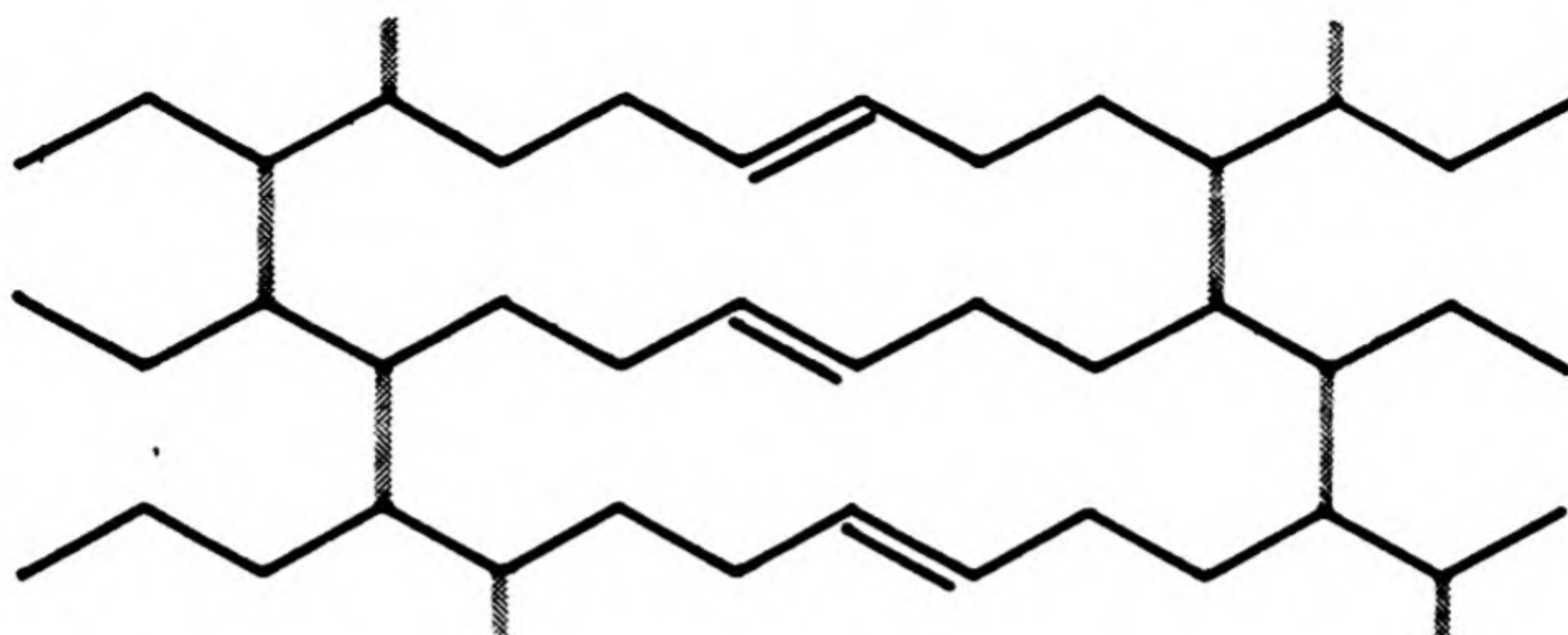
The unsaturated linkages remaining in the chain can also enter into polymerization chains. This ties two or more chains together, and is called cross-linking. A large number of cross-links bind the polymer chains into a three-dimensional network. Such a network is very rigid, resulting in a hard resin (see Fig. 46-2).



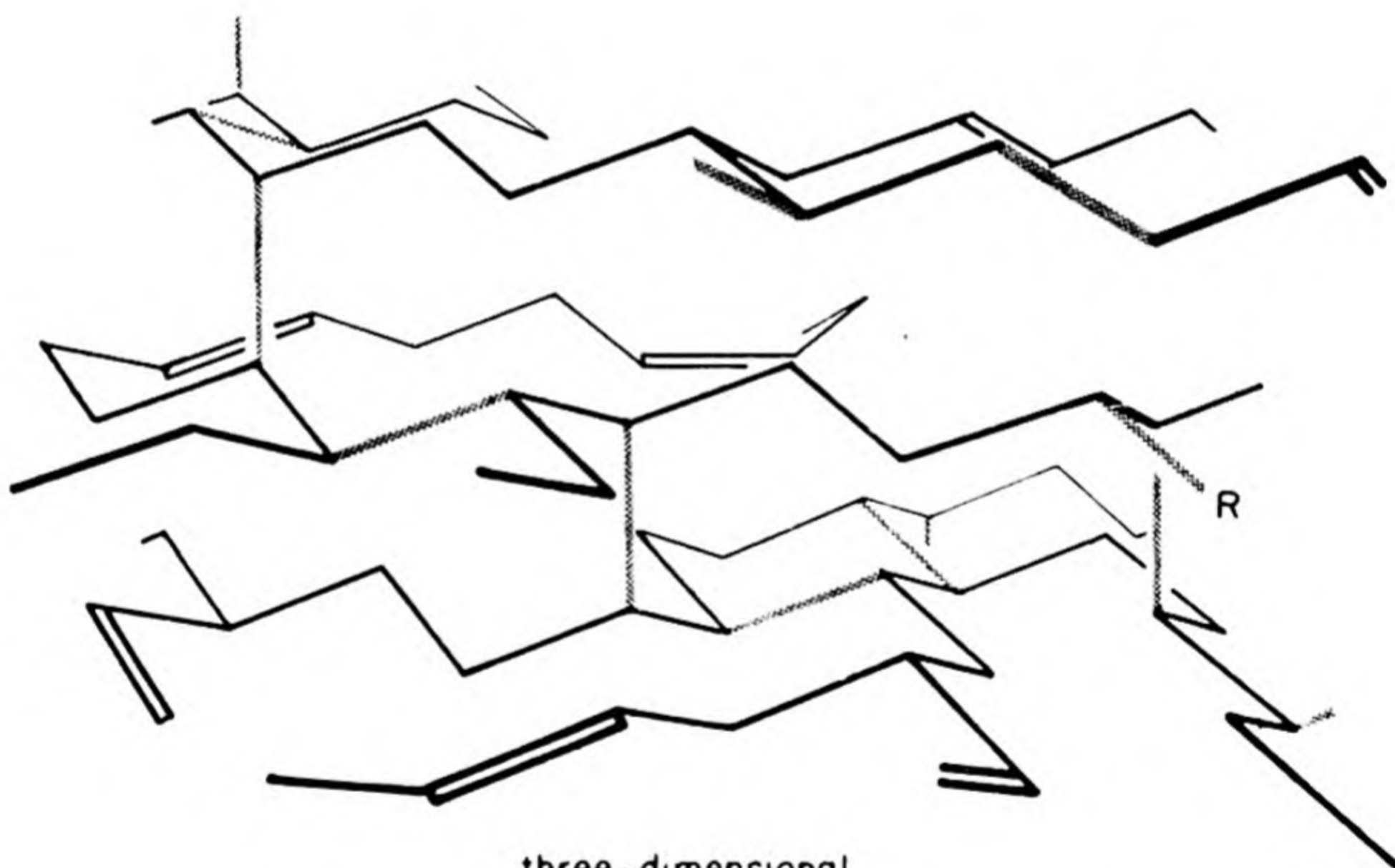
(7) *Copolymers and Copolymerization.* A polymer need not be made up of only one kind of monomer unit. Several polymeric materials of commercial value are made up of two kinds of units. Such substances are called *copolymers*. Their formation is called *copolymerization*.

Steps in copolymerization are the same as those in simple polymerization. However, propagation steps are of considerable interest. The rates of copolymerization are complicated by the relative reactivities of the two monomers, \mathbf{m}_1 and \mathbf{m}_2 , and the relative reactivities of the radicals terminating in units from these monomers, $\mathbf{p}_1\cdot$ and $\mathbf{p}_2\cdot$ ($\mathbf{p}_1\cdot = \text{R}-\mathbf{m}_1\cdot$ and $\mathbf{p}_2\cdot = \text{R}-\mathbf{m}_2\cdot$), as well as the concentrations of each of these species. Rate constants of the reactions are represented by \mathbf{k} .





two-dimensional analogy



three-dimensional

Fig. 46-2. Idealized Cross-Linked Polymer Network

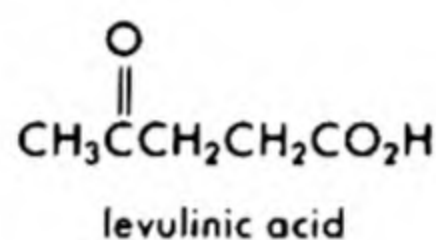
Several extreme cases exemplify the varied results that can be obtained in copolymerization.

If $k_{11} \gg k_{12}$ and $k_{22} \gg k_{21}$, the two monomers polymerize at the same time, and cross over occasionally to form chains consisting of long blocks of the same kind of monomer. Such substances are called *block copolymers*. If the reverse is true, and $k_{12} \gg k_{11}$, $k_{21} \gg k_{22}$, each rad-

to heat and oxidation. From this simple beginning came the complex rubber technology of today.

Besides vulcanizing agents, modern rubber uses a multitude of materials termed accelerators, activators, antioxidants, retarders, fillers, peptizing agents, stiffeners, and pigments. Special purposes require blowing agents (for foaming), emulsion stabilizers (for latexes), softeners, and odorants.

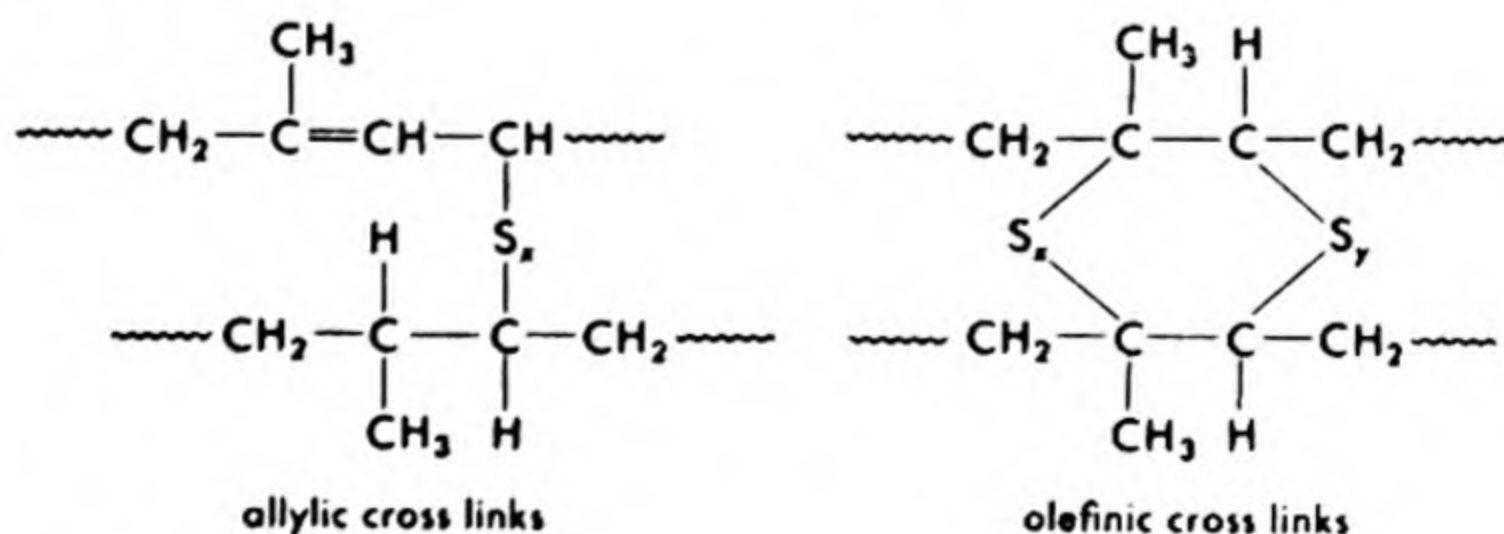
The structure of natural rubber was in part deduced from its ozonolysis to levulinic acid. The molecular weights of the polymeric molecules vary from about 100,000 to several million.



B. Cross-Linking and Vulcanization

The treatment of rubber or of a rubber-like material to join polymeric molecules together is called *vulcanization*. Cross-linking the linear molecules (see Fig. 46-2) makes a three-dimensional polymeric network and causes profound changes in physical properties. Natural rubber is soft, thermoplastic (melts when heated), and readily soluble in benzene. Slightly cross-linked material is harder, higher-melting, and less soluble. When many cross-links are present (hard rubber), the material becomes brittle and completely insoluble. For useful purposes, control of the amount of cross-linking or vulcanization is, therefore, essential.

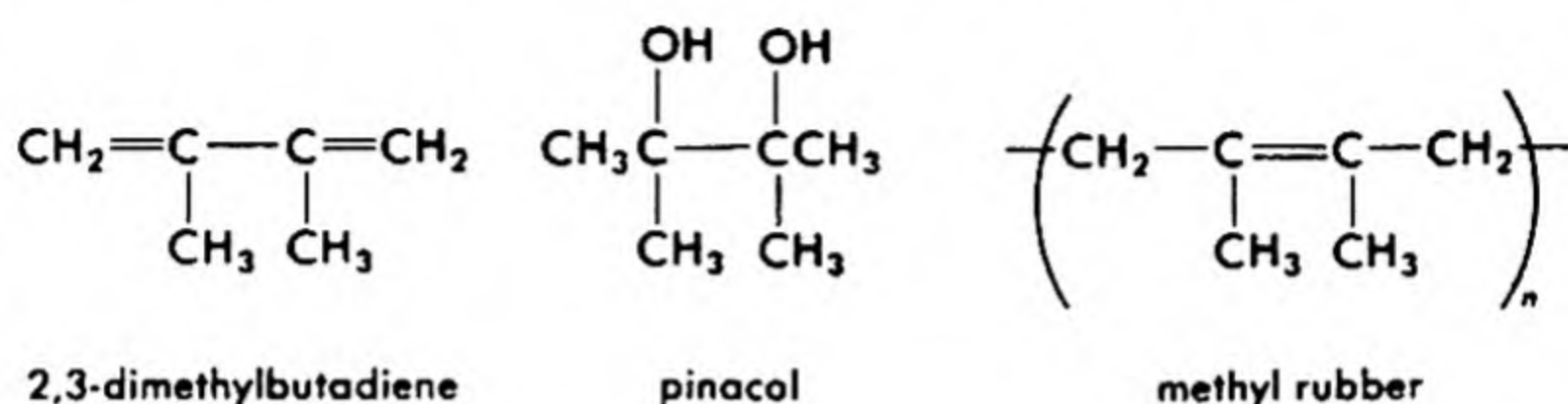
Vulcanization of rubber with sulfur is believed to involve the formation of free radicals in the rubber molecule by attack of sulfur fragments with the allylic hydrogen atoms or with the double bonds to give cross-links of the type shown below, as well as more complicated reactions. In vulcanization to give tire-tread rubber, less than 1% of the isoprene units are cross-linked.



C. Synthetic Rubbers

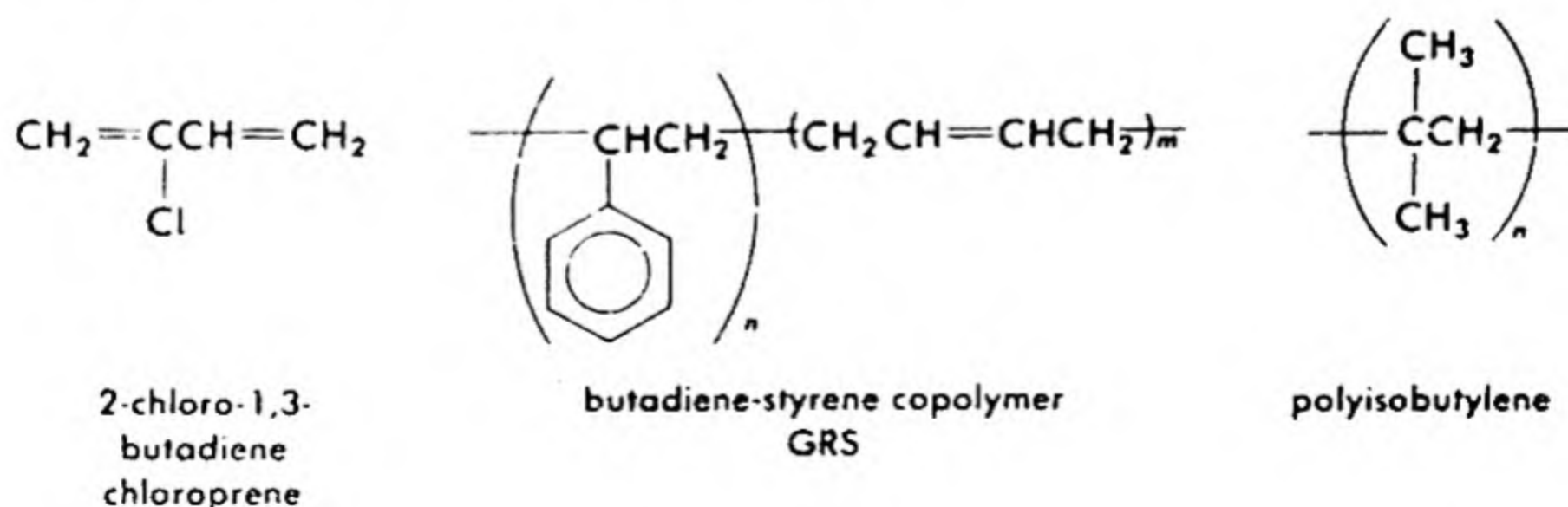
Shortages of natural rubber, price factors, and limitations in the properties of natural rubber stimulated the development of synthetic rubbers.

During World War I, when the Allied fleets blockaded the German powers and cut them off from East Indian supplies, German chemists developed the first industrial synthetic rubber. Isoprene was not available, but 2,3-dimethylbutadiene could be prepared by dehydration of pinacol. The elastomer produced by polymerization of this material was called



methyl rubber. While it was deficient in many properties, it was used during World War I.

Study of the preparation of elastomers continued during the period from 1920 to 1940 and was enhanced during the late 1930's and early 1940's by the possible (and later actual) loss of control of Far Eastern sources of natural rubber to the Japanese. The first synthetic rubber that was developed with properties superior to natural rubber was polychloroprene, in which the monomer was 2-chlorobutadiene. The polymer, called *Neoprene*, has much more oil-resistance than natural rubber. Butadiene became available on a large scale by dehydrogenation of *n*-butane (see §28-II) and was polymerized with sodium to give a rubber-like material, which was called *Buna* (*butadiene* + *natrium*) *rubber* by the German chemists who produced it. It was observed that copolymers of butadiene with styrene gave particularly useful materials. This copolymer, containing about 75% butadiene and 25% styrene and produced by free radical polymerization, was developed during World War II, and is called GRS (government rubber styrene). Almost all automobile tire treads contain this material. In the early 1960's it was found that isoprene could be polymerized by coordination or anionic polymerization to give stereoregular polymers. This means that polyisoprene which is almost identical with natural rubber can now be produced.



Vulcanization of natural rubber utilizes only a small fraction of the unsaturated sites in the polymer chain. The remaining double bonds contribute to the physical and chemical properties of rubber, but are also sites for degradation of rubber (ozonolysis, oxidation, photochemical reactions). *Polyisobutylene* has no unsaturation, and so is chemically inert toward both vulcanization and degradation reactions. A copolymer of isobutylene with 1–2% of a diene, such as butadiene or isoprene, gives a polymer which resists degradation but which has enough unsaturation to allow cross-linking. The polymer, called *butyl rubber*, has an unexpected bonus property—it is relatively impervious to gases—so that it has replaced natural rubber for use in tire tubes.

It would appear that copolymers of ethylene, propylene, and a small amount of a diene component will become important as a relatively saturated (but vulcanizable) elastomer called EPT rubber (ethylene-propylene-terpolymer). Various unconjugated dienes can be used to provide the residual double bonds for vulcanization.

46-3 PLASTICS

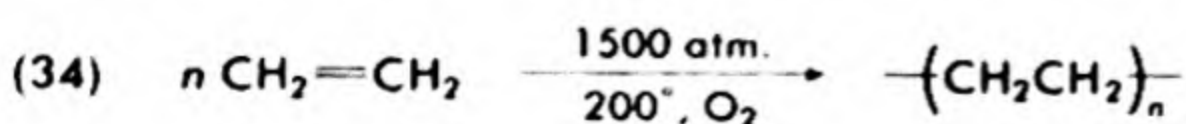
Elastomers (rubbers) are materials which deform readily and return to their original shapes afterward.

Plastics (resins) are materials with dimensional stability such that they are not readily deformed at the temperature at which they are used. They are hard, horny, or glassy materials. They are further classified into *thermoplastic resins*, which soften on heating and can be molded, and *thermosetting resins*, which set permanently to hard masses once formed by heating. *Chemisetting resins* are those which set to infusible material without heating, but rather upon application of the proper reagents or catalysts. They may be used as textile fibers, films, adhesives or as molded objects.

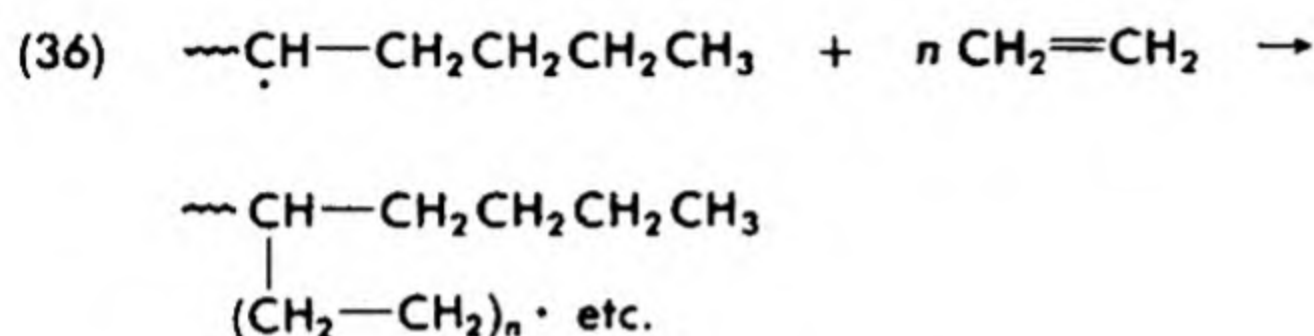
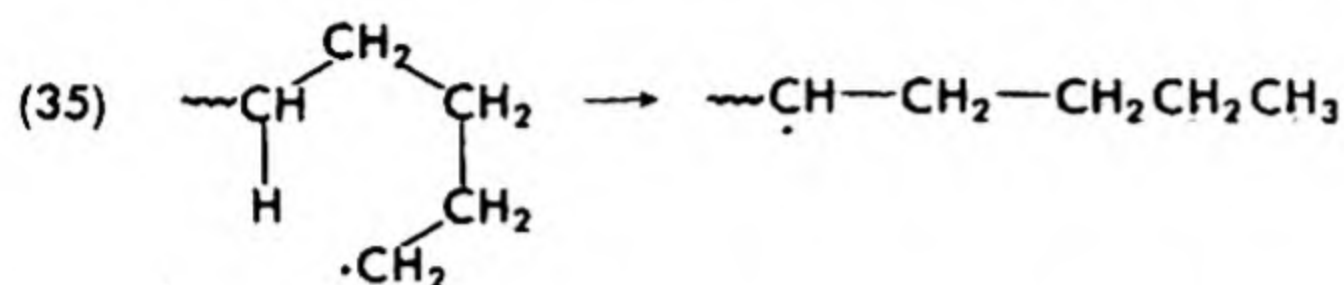
Much more satisfactory than the above operational classification is the chemical classification of polymers according to the method of formation (discussed in §46-1) or according to the chemical groups involved. The ensuing polymers or copolymers provide almost unlimited variety in properties. In fact, however, only a limited number have been exploited commercially, because of cost or usefulness factors. Some of the most useful are discussed below.

A. Polyethylene

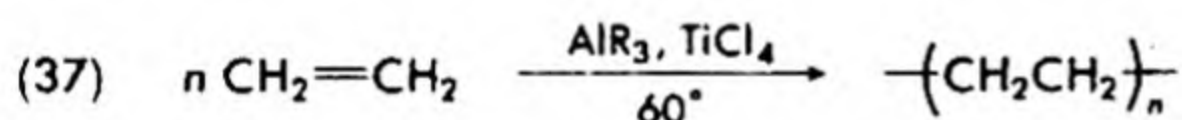
The first commercial process for the polymerization of ethylene utilized high pressure and temperature (eq. 34) and was a free radical process



catalyzed by traces of oxygen. This type of polyethylene has considerable branching largely caused by "back-biting" of the free radical end onto carbon-hydrogen bonds on the chain (eqs. 35 and 36).



The branches average four carbons in length and lower the crystallinity of the polymer (packing of chains is not as uniform), making this polyethylene lower-melting than that produced by coordination polymerization (eq. 37). Coordination polymerization produces polyethylene at lower temperatures and low pressure. The product is more crystalline and melts above 100°. Polyethylene is used as a film and also for molded products.

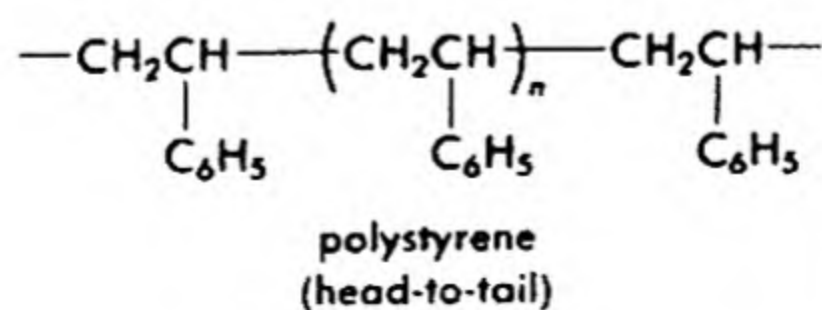


B. Other Aliphatic Polyolefins

Propylene is polymerized by coordination polymerization to isotactic (§46-1A(6)) *polypropylene*, which has begun to find use as a textile fiber. *Polyisobutylene*, produced by cationic polymerization (§46-1A(2)), is used as a relatively low molecular weight polymer (M.W. $\sim 50,000$) as an adhesive and as an additive to increase the viscosity of lubricating oils.

C. Polystyrene

Free-radical-polymerized polystyrene is a relatively inexpensive polymer. It is clear and colorless and finds much use in molded products as well as in foams. It is an atactic polymer, softening at 85°. Isotactic polystyrene, produced by coordination polymerization, melts at 250°. Both have the head-to-tail structure, as do most vinyl polymers.

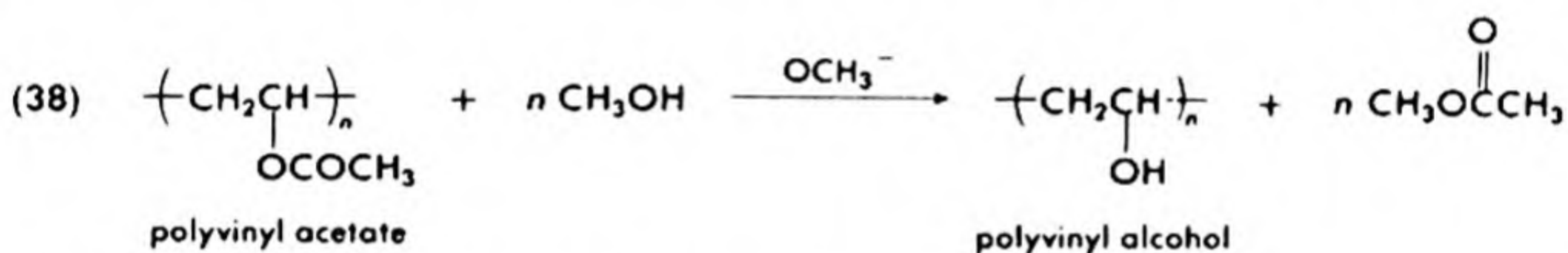


D. Haloethylene Polymers

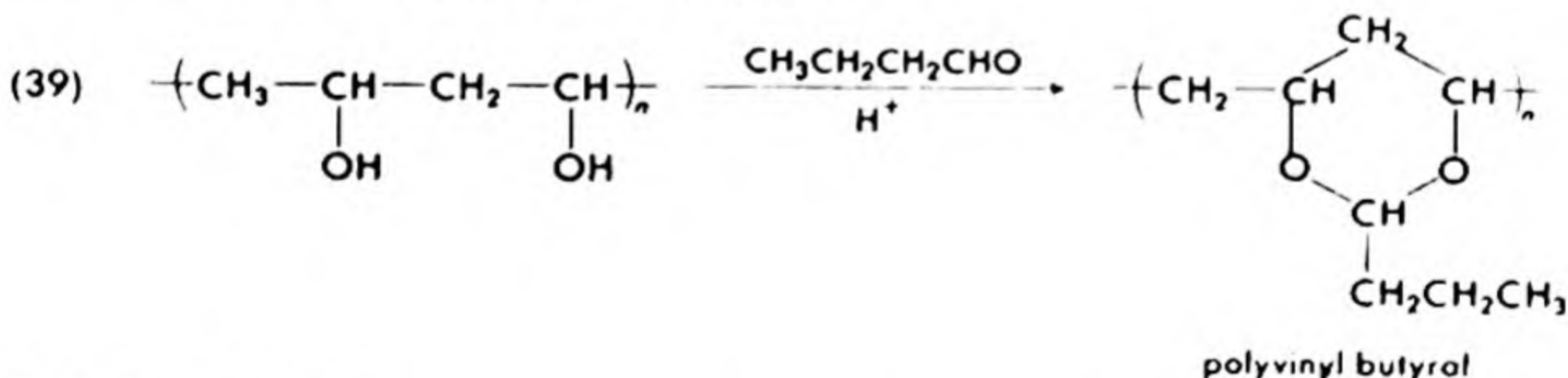
Free-radical-polymerized polyvinyl chloride ($\text{CH}_2=\text{CHCl}$) is a tough, flexible plastic material used as coatings, films, and molded products. Under trade names such as Koroseal and Vinylite it finds use in rainwear, shower curtains, etc. Copolymerization of vinylidene chloride ($\text{CH}_2=\text{CCl}_2$) with small amounts of vinyl chloride gives the tough film Saran. Radical polymerization of tetrafluoroethylene ($\text{CF}_2=\text{CF}_2$) gives a chemically inert, tough, high temperature-stable polymer, Teflon.

E. Polymers from Unsaturated Esters

Polymerization of methyl acrylate, $\text{CH}_2=\text{CHCOOCH}_3$, of methyl methacrylate, $\text{CH}_2=\text{C}(\text{CH}_3)\text{COOCH}_3$, or copolymerization of the two gives clear, transparent resins which can be used as shatterproof optical lenses, shields, aircraft "glass," and dentures. The polymers carry the well-known trade names Lucite and Plexiglas. Polyvinyl acetate, prepared from the monomer $\text{CH}_2=\text{CHOCOCH}_3$, is a soft, rubbery polymer and is used as an adhesive. Copolymers of vinyl acetate and vinyl chloride are used as tough coatings. Methanolysis of polyvinyl acetate converts the polymer to polyvinyl alcohol, a water-soluble polymer (eq. 38). Treatment of polyvinyl alcohol with aldehydes gives polyacetals (eq. 39). With



n-butyraldehyde (eq. 39) the polyvinyl butyral which results is a tough adhesive used in laminated safety glass.



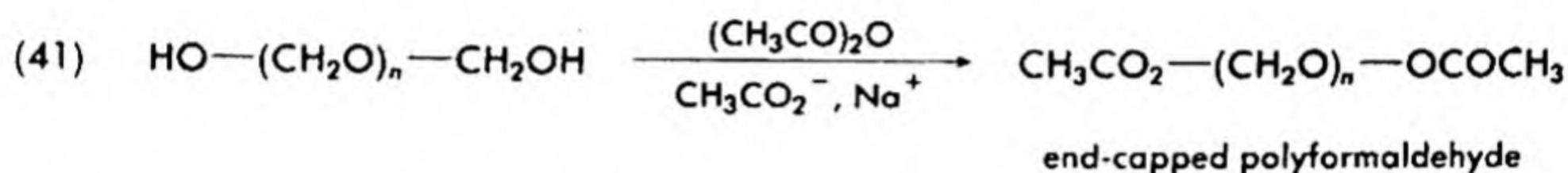
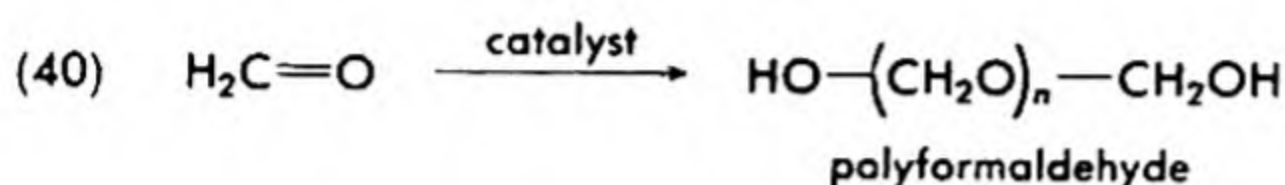
F. Polyacrylonitrile

Polymerization of acrylonitrile ($\text{CH}_2=\text{CHC}\equiv\text{N}$) gives a polymer which finds considerable use as a textile fiber. Trade names used are Orlon and Acrilan.

G. Polymers with Hetero Atoms in the Chain

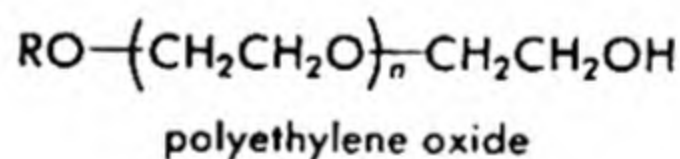
All of the polymers described above have only carbon atoms in the backbone of the polymer. Many useful polymers have oxygen, nitrogen,

or other atoms in the backbone. Most of these are produced by reactions that might best be classified as condensation reactions, which are discussed below along with related substances produced by addition reactions. In this section we will discuss only polyethers prepared by addition polymerization involving on the one hand, the carbon-oxygen double bond of formaldehyde, and on the other hand, ring opening of the ethylene oxide three-membered ring. Polymerization of formaldehyde (eq. 40) gives a polymer, which is stabilized by capping the hydroxyl end groups with acetic anhydride (eq. 41). Unstabilized *polyformaldehyde* readily



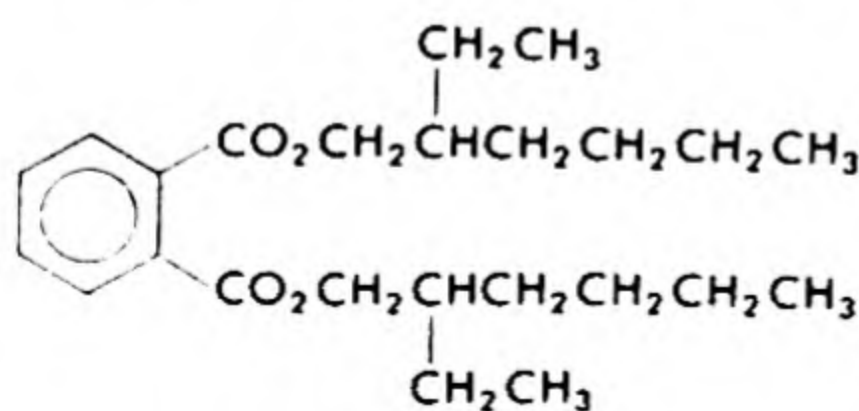
depolymerizes on treatment with acid and heat, but capping gives a tough resin (trademark Delrin).

Polyethylene oxides are prepared by ionic catalysis from ethylene oxide. The general structure is given below. Unless the end group R is very large, the polymers have some water solubility. These polymers have trademarks Carbowax and Igepal.

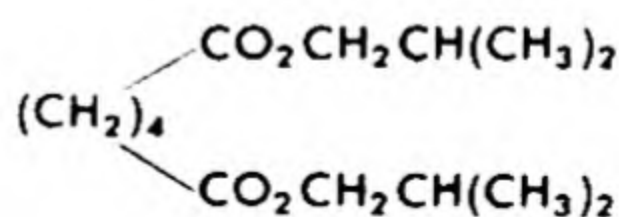


46.4 PHYSICAL MODIFICATION OF POLYMERS

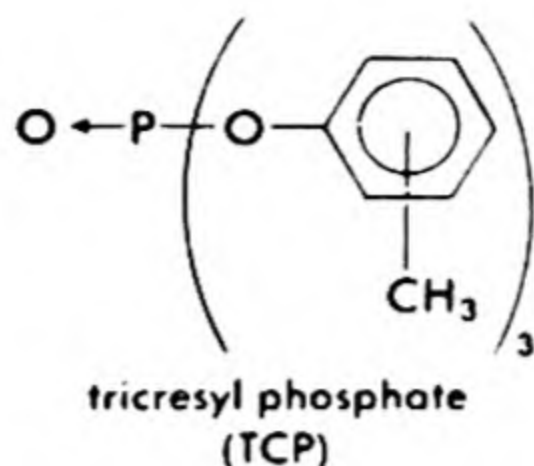
Resins are often too brittle for use and require addition of materials called *plasticizers*. The plasticizer acts like a solvent during the molding, allowing softening at somewhat lower temperatures and letting the polymer molecules line up with each other more favorably to eliminate internal stresses. This gives improved toughness and workability to the product. Because subsequent loss of a plasticizer would cause shrinkage, embrittlement, and deformation of a molded object, the plasticizer must be nonvolatile and must not be lost in other ways from the object. Plasti-



2-ethylhexyl phthalate



isobutyl adipate



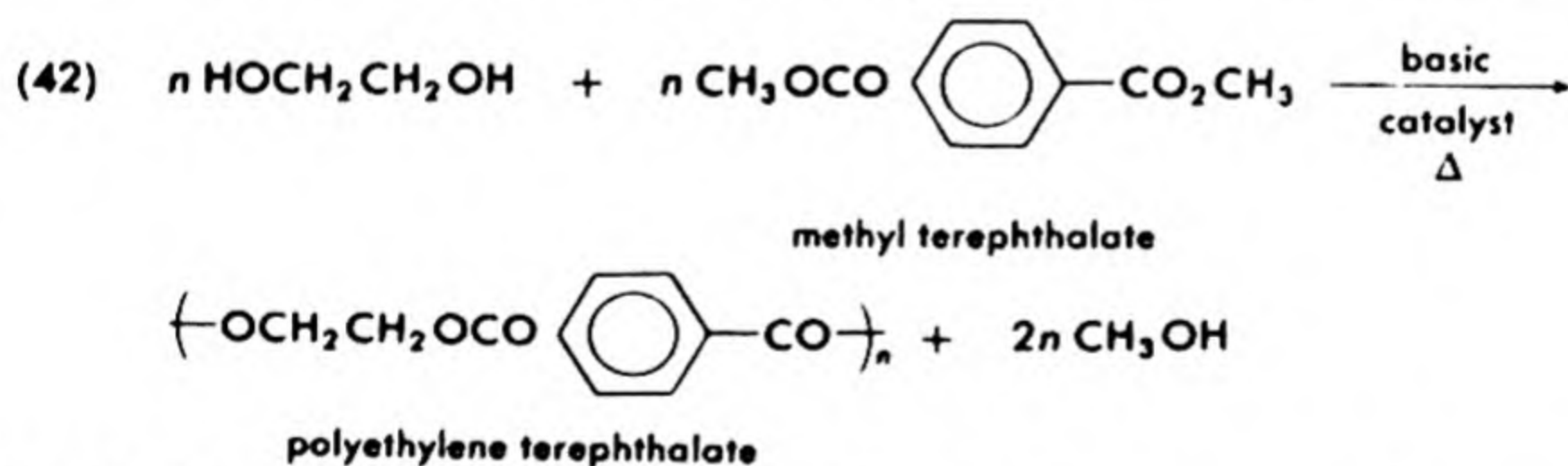
cizers must be inexpensive, stable, and compatible with the polymer. Most of the common ones are esters. Typical examples are dioctyl phthalate (2-ethylhexyl phthalate), isobutyl adipate, and tricresyl phosphate.

46-5 CONDENSATION POLYMERS

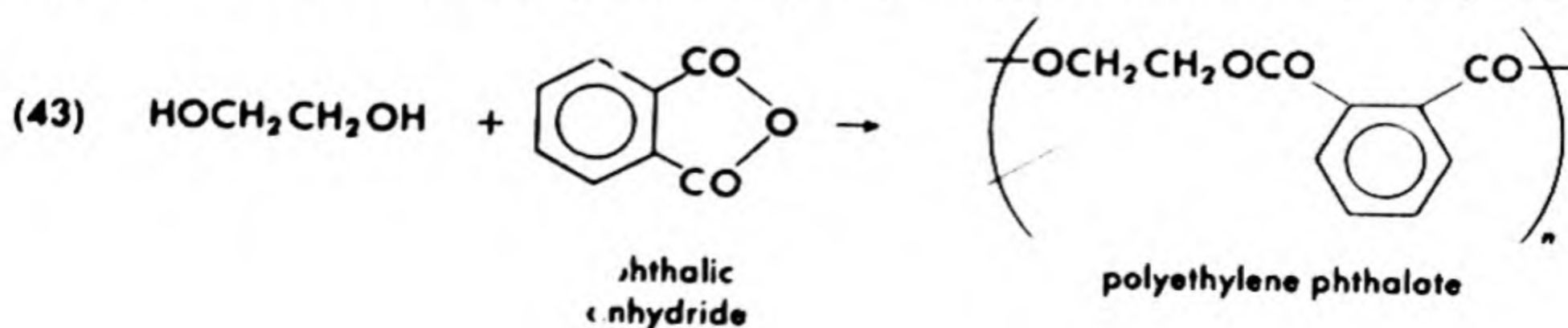
The polymers discussed thus far are prepared by addition reactions, largely involving multiple bonds. Many important polymers are formed by condensation reactions in which monomers react to form polymers with the loss of a small molecule in the formation of the new bonds. Certain other polymers formed by ring-opening reactions or addition reactions are also considered here because of their structural relationship to condensation polymers.

A. Polyesters

Esterification reactions between polyols and polybasic acids or acid derivatives lead to polymer molecules. If the alcohol is a diol and the acid is dibasic, a linear polymer results. An important example is given in eq. (42), where ester interchange between ethylene glycol and methyl terephthalate gives *polyethylene terephthalate*. This material used as a



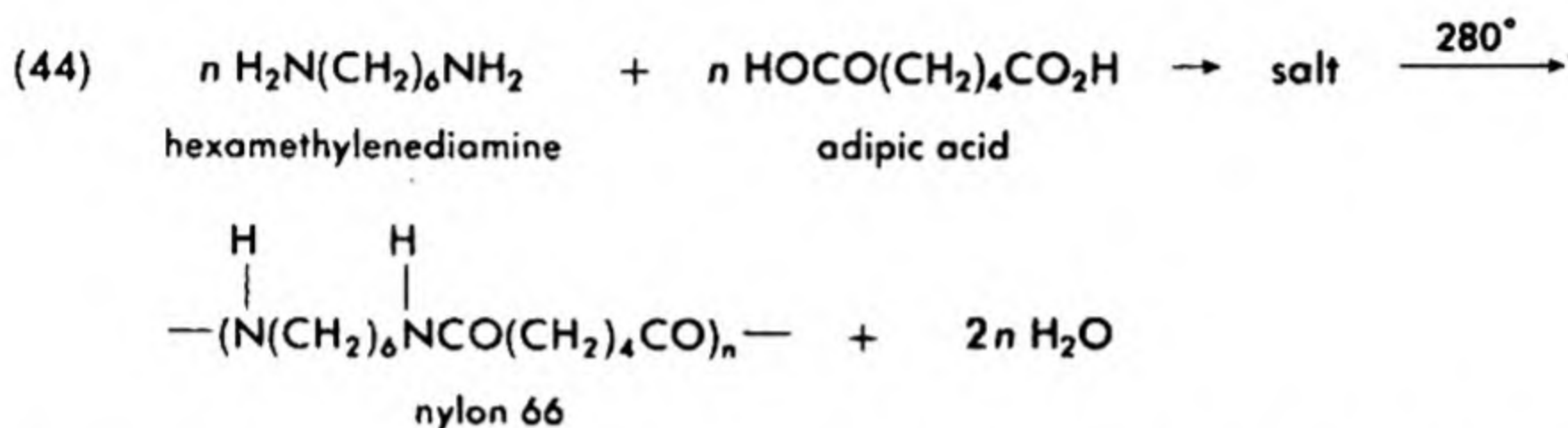
textile fiber is sold under the trademarks Dacron and Terylene and as a film as Mylar. Ethylene glycol and phthalic anhydride give a useful molding resin which is thermoplastic (eq. 43). If glycerol is used, the product



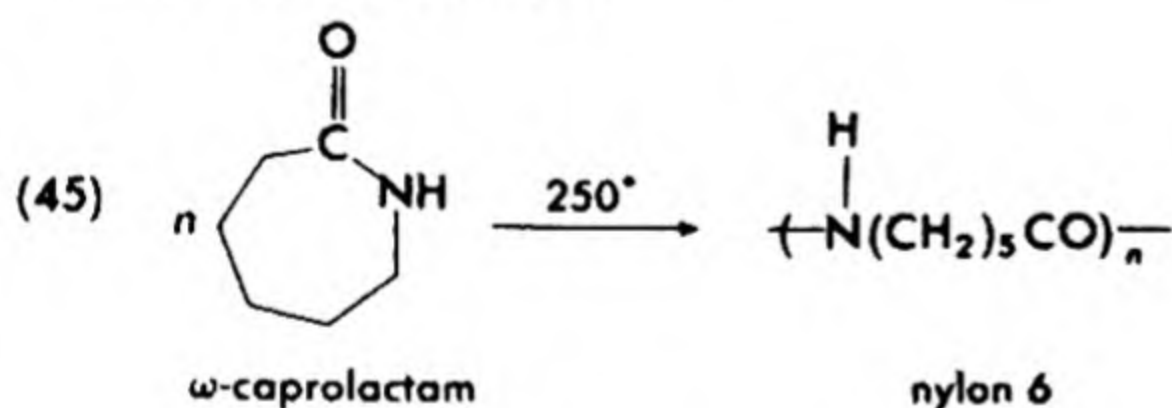
is a three-dimensional polymer and is infusible. A partly polymerized material is used as a thermosetting molding agent. These are called *alkyd resins*.

B. Polyamides

The thermal decomposition of salts of diamines and dicarboxylic acids leads to the formation of polyamides. Such a reaction led to the synthesis of the first completely synthetic commercial textile fiber by Wallace Carothers of E. I. du Pont de Nemours and Company. It was produced from hexamethylenediamine and adipic acid (eq. 44). The polymer is called *nylon 66*. (The first 6 refers to the number of carbon atoms in the

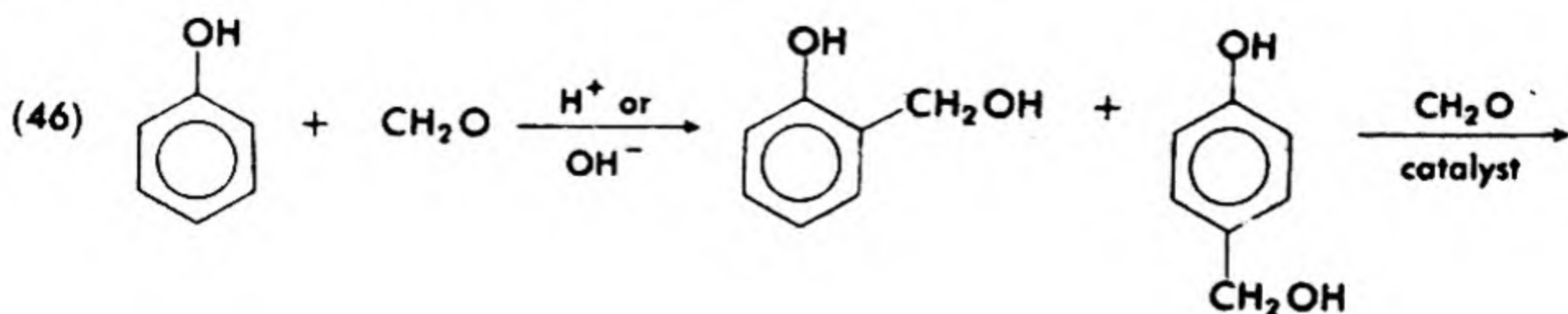


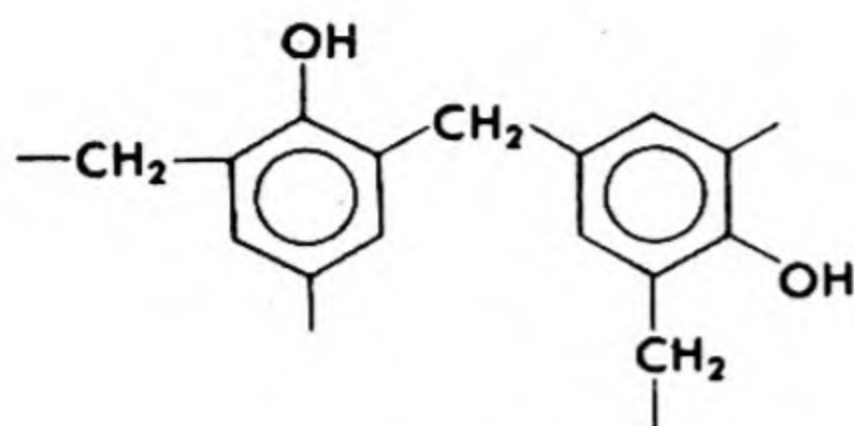
amine and the second to the number in the acid.) It is used as a fiber for fabrics, tire cords, and ropes as well as for molded objects. Nylon 610, prepared from hexamethylenediamine and sebacic acid, $\text{HOCO}(\text{CH}_2)_8\text{CO}_2\text{H}$, is also used on a large scale. *Polycaprolactam*, prepared by the ring-opening polymerization of caprolactam (eq. 45), is called nylon 6 and is used in textiles.



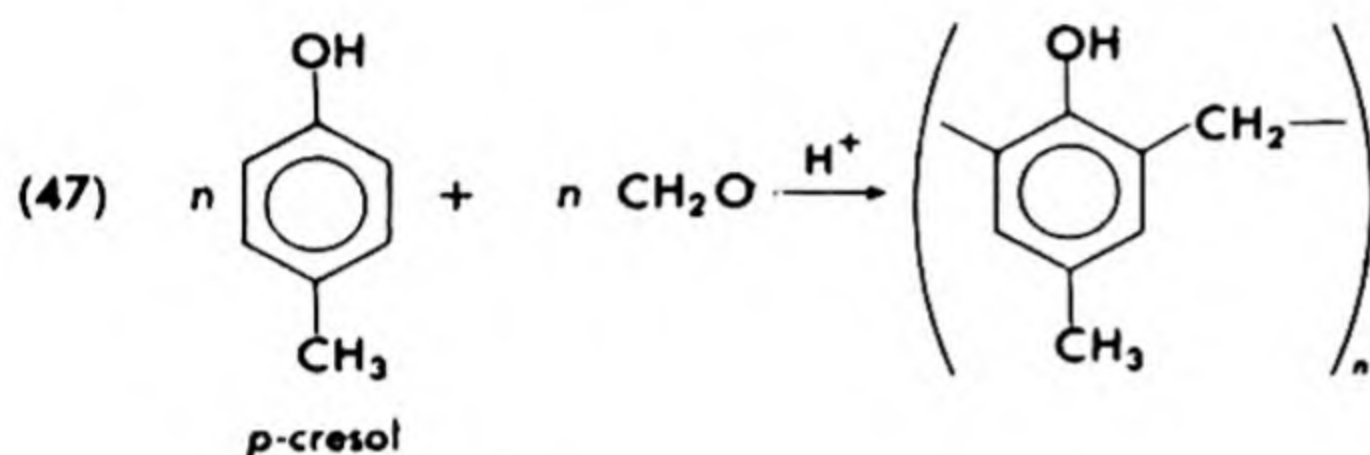
C. Phenol-Formaldehyde Polymers

Treatment of phenol with formaldehyde in the presence of small amounts of acids or bases gives thermosetting resins. The initial reactions involve the formation of hydroxymethylphenols and polyhydroxymethylphenols which then react further (outline 46).

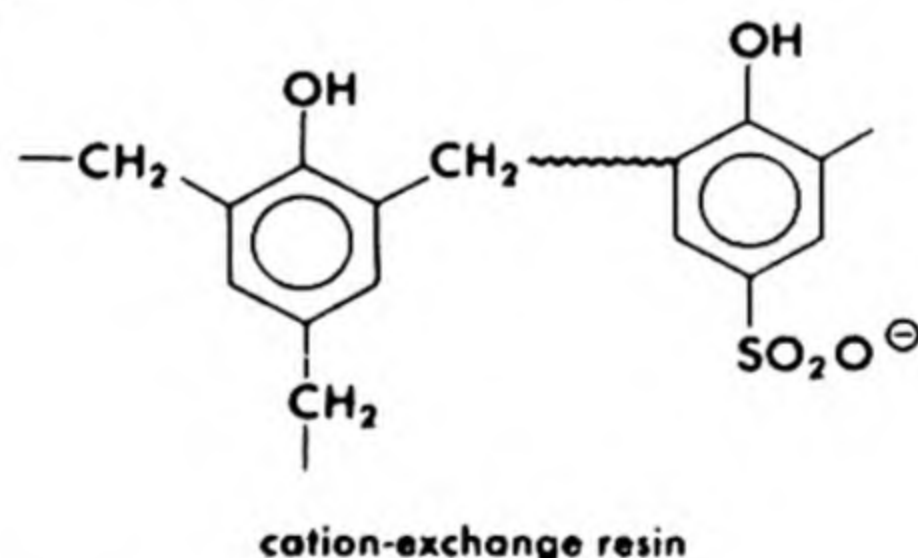




Bakelite is an example of such a resin. When resorcinol is substituted for phenol, an adhesive is produced. If one of the *ortho* or *para* positions in the phenol is blocked, a linear polymer results (eq. 47). This polymer can be cross linked by copolymerization with small amounts of phenol. When

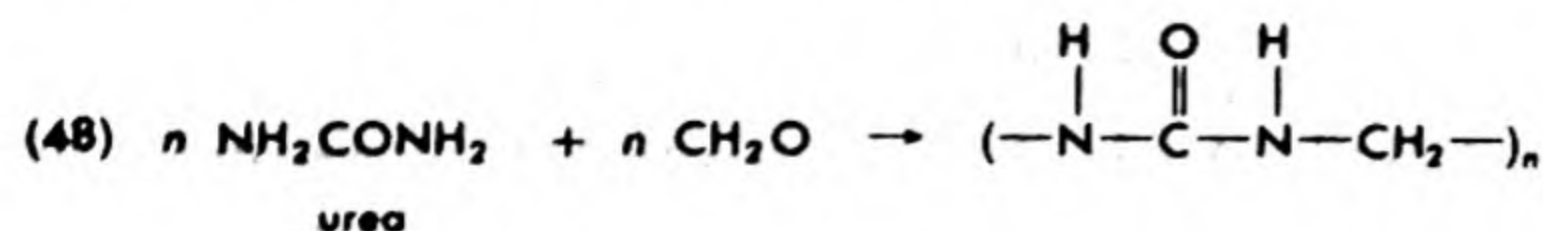


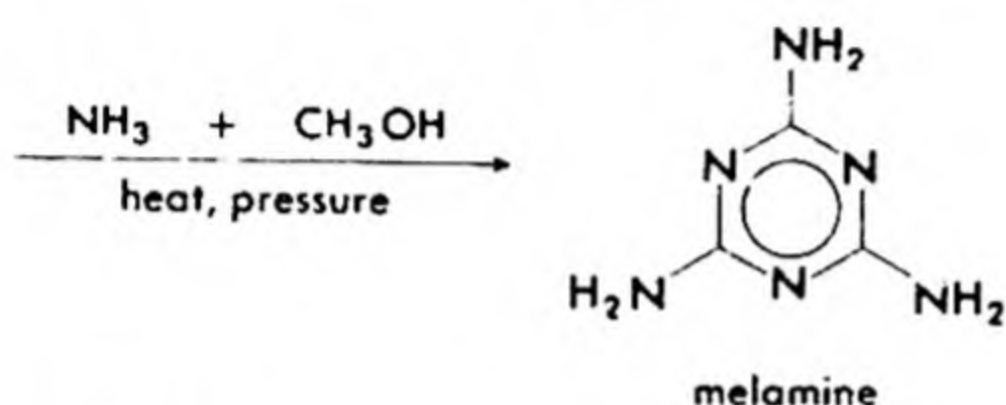
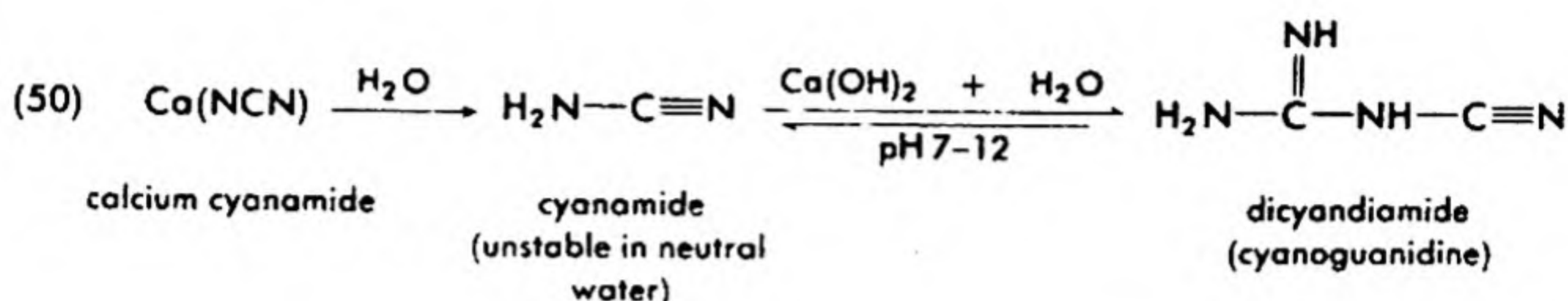
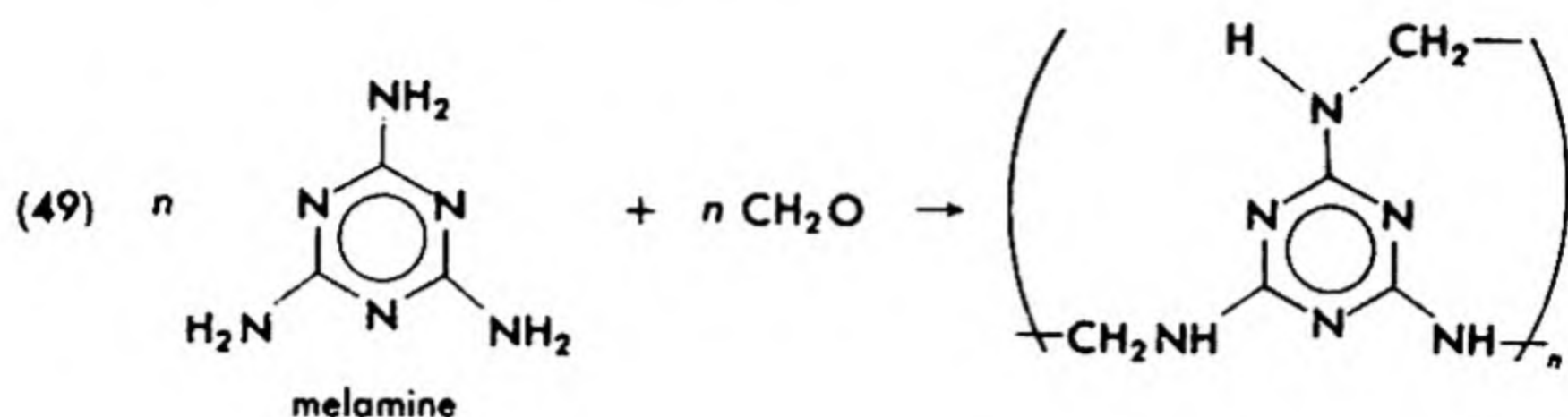
p-phenolsulfonic acid is copolymerized with phenol and formaldehyde, a cation-exchange resin is formed. Other aldehydes may be used rather than formaldehyde.



D. Amine- and Amide-Formaldehyde Polymers

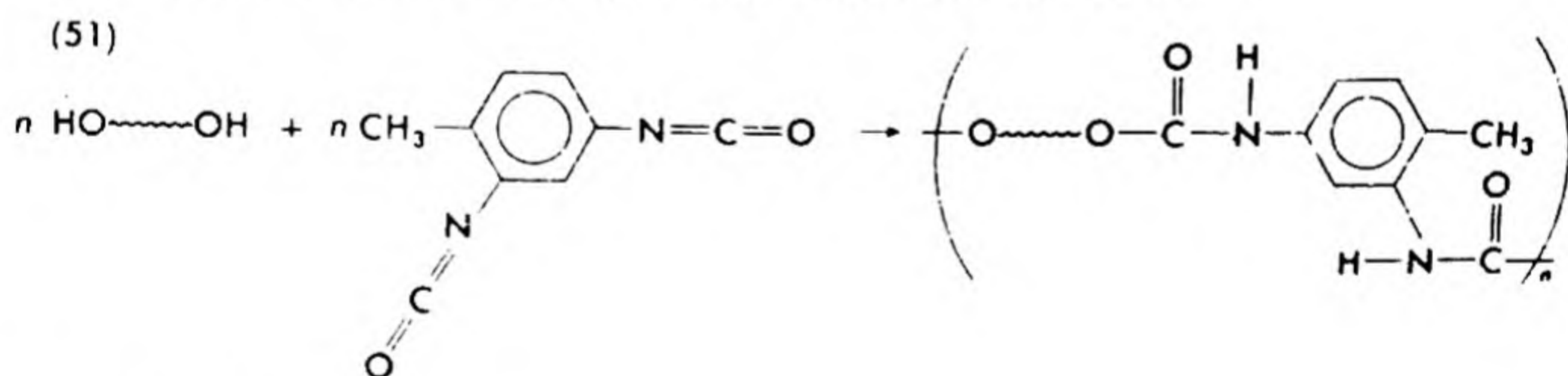
Useful resins are produced by using polyfunctional amines and amides with formaldehyde. Thus, urea and formaldehyde gives a polymer (eq. 48) with a trade name Beetle. Although a linear structure is shown, there is considerable cross-linking in the polymer. A similar thermosetting polymer, Melmac, is formed from melamine and formaldehyde (eq. 49). Melamine is produced as indicated in outline (50).





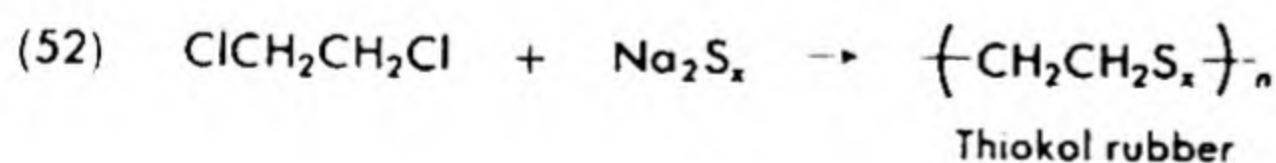
E. Polyurethanes

Diisocyanates on treatment with diols give polyurethanes. A large variety of diols are used. A general equation, using toluene diisocyanate, is given in eq. (51). The materials are used to make rigid or flexible foams or rubber-like materials, depending on the diol involved.



F. Polysulfide Elastomers

When ethylene chloride and sodium polysulfide are allowed to react (eq. 52), an oil-resistant rubbery polymer is produced. This is called Thiokol rubber.



SUPPLEMENTARY READINGS

Button, D. W., "Building a Natural Rubber Latex Compound," *J. Chem. Educ.*, **34**, 255-259 (1957).

- Ferington, T. E., "Kinetics of Polymer Formation by Free Radical Mechanism," *J. Chem. Educ.*, **36**, 174-181 (1959).
- Fettes, E. M., and J. S. Jorczak, "Polysulfide Polymers," *Ind. Eng. Chem.* **42**, 2217-2223 (1950).
- Fisher, H. L., "New Horizons in Elastic Polymers," *J. Chem. Educ.*, **37**, 369-377 (1960).
- Flory, P. J., *Principles of Polymer Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, Chapters 4, 5, and 6.
- Marvel, C. S., *An Introduction to the Organic Chemistry of High Polymers*, Wiley, New York, 1959.
- Powers, P. O., "Phenol-, Urea- and Melamine-Formaldehyde Plastics," *Ind. Engr. Chem.*, **45**, 1063-1066 (1953).
- Powers, P. O., "Plastics, Resins and Rubbers," *Chem. Eng. News* **24**, No. 20 2784-2788 (1946).
- Reynolds, W. B., "Cold Rubber," *J. Chem. Educ.* **27**, 494-499 (1950).
- Sorenson, W. R., and T. W. Campbell, *Preparative Methods of Polymer Chemistry*, Interscience, New York, 1961.
- Staff Report, "Urethane Plastics—Polymers of Tomorrow," *Ind. Engr. Chem.* **48**, 1383-1391 (1956).
- Stille, J. K., *Introduction to Polymer Chemistry*, Wiley, New York, 1962.
- Tobolsky, A. V., "Revolution in Polymer Chemistry," *Am. Scientist* **45**, No. 1, 34-43 (1957).
- Walling, C., *Free Radicals in Solution*, Wiley, New York, 1957, Chapters 3, 4, and 5.

QUESTIONS AND PROBLEMS

1. Give an explanation, illustration, or definition to show clearly what is meant by each of the following terms. Accompany diagrams with verbal explanation.

- | | |
|--------------------------------|-------------------------|
| a. addition polymerization | i. initiator |
| b. branched polymer | j. isotactic polymer |
| c. chain transfer | k. linear polymer |
| d. condensation polymerization | l. monomer |
| e. copolymerization | m. plasticizer |
| f. cross-linked polymer | n. syndiotactic polymer |
| g. graft polymer | o. vulcanization |
| h. inhibitor | |

2. Write out a formulated representation of each of the steps involved in the polymerization of the following materials. Use structural formulas of actual compounds. Parallel each step with the abbreviated general symbolism for the step.

- | | |
|---|---------------------------------------|
| a. styrene, using benzoyl peroxide | c. cyclohexene, using sulfuric acid |
| b. propylene, using triisopropyl aluminum; using titanium tetrachloride | d. chloroprene, using benzyl peroxide |

3. Show how the following compounds can be prepared from the indicated raw materials and inorganic reagents. Use structural formulas or ring symbols to represent organic compounds. Indicate necessary inorganic reagents and special conditions.

- a. polyvinyl acetate from acetylene
- b. polymethyl methacrylate from acetone and methanol
- c. a phenolic resin from *o*-cresol and formaldehyde
- d. a polyurethane from polyethylene glycol averaging ten units, 2,4-tolylene-diamine and a suitable catalyst
- e. a nylon from azelaic acid and hexamethylenediamine

4. Show how the following raw materials for plastics and rubbers can be prepared from methane, ethylene, propylene, acetylene, benzene, toluene, and inorganic reagents. Indicate essential reagents and special conditions.

- | | |
|------------------------------------|---|
| a. chloroprene | e. methyl methacrylate |
| b. 2,4-toluene diisocyanate | f. <i>N,N'</i> -diphenyl- <i>p</i> -phenylene-diamine |
| c. epichlorohydrin | |
| d. <i>p,p'</i> -methylenedianiline | |

5. Show how adipic acid and hexamethylenediamine can be prepared from phenol.



List of Reference Works for Organic Chemistry

A single textbook can provide only a bare introduction to a subject. Anyone who intends to utilize organic chemistry as a body of knowledge must learn to supplement the basic textbook material with the many advanced and specialized texts, some of the more important of which are listed here; others are listed in the Supplementary Readings. Another necessity is the ability to refer to original research papers in the periodicals listed in §I-1. The list is not exhaustive, but includes those of primary interest to the organic chemist. The portions of the titles in boldface correspond to *Chemical Abstracts* abbreviations. Indexing and abstracting works which serve as the key to finding a particular subject or the work of a particular author are listed in §I-2.

I-1 ORIGINAL LITERATURE

Angewandte Chemie, Verlag Chemie, G.m.b.H.

Annalen der Chemie, Justus Liebig's, Verlag Chemie, G.m.b.H.

Biochemical Journal, Cambridge University Press

Bulletin de la Société Chimique de France, Masson et Compagnie.

Canadian Journal of Chemistry, National Research Council, Canada.

Chemische Berichte, Verlag Chemie, G.m.b.H.

Helvetica Chimica Acta, Basel 7, Switzerland.

Industrial and Engineering Chemistry, American Chemical Society.

Journal of Biological Chemistry, American Society of Biological Chemists.

Journal of General Chemistry of the U.S.S.R. (English Translation), Consultants Bureau.

Journal of Organic Chemistry, American Chemical Society.

Journal of the American Chemical Society.

Journal of the Chemical Society (London), Burlington House.

Recueil des travaux chimiques des Pays-Bas, Nederlandse Chemische Vereniging

Tetrahedron Letters, Pergamon Press (London).

Zeitschrift für Physiologische Chemie, Hoppe-Seylers, Walter de Gruyter and Co.

Zhurnal Obschei Khimii, Izdatel' stvo Akademii Nauk S.S.S.R.

I-2 GENERAL REFERENCE WORKS: indices to the chemical literature.

Chemical Abstracts, Americal Chemical Society (with annual and decennial indices; covers chemical literature 1906–1956; pentennial indices from 1961)

Chemisches Zentralblatt, published by Deutsche chemische Gesellschaft until 1945, now by the joint effort of several German Chemical societies (German equivalent of *Chemical Abstracts*; with cumulative indices every few years to 1939; covers chemical literature since the year 1830)

Beilsteins Handbuch der organischen Chemie, Springer-Verlag, Berlin. (Main volumes and two supplements list all organic compounds known to 1929. Third supplement is in preparation; some volumes are published.)

I-3 ENCYCLOPEDIAS, DICTIONARIES, HANDBOOKS

Gowan, J. E., and T. S. Wheeler, *Name Index of Organic Reactions*, Wiley, New York, 1960.

Handbook of Chemistry and Physics, 45th ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1964–1965 (revised biennially).

Heilbron, I. M., *Dictionary of Organic Compounds*, 4th ed., Oxford University Press, New York, 1965.

Krauch, H., and W. Kunz, *Organic Name Reactions*, Wiley, New York, 1963.

Lange, N. A., *Handbook of Chemistry*, 10th ed., McGraw-Hill, New York 1961 (revised about every four years).

Patai, S., *Glossary of Organic Chemistry, Including Physical Organic Chemistry*, Wiley, New York, 1962.

Patterson, A. M., L. T. Capell, and D. F. Walker, *The Ring Index*, 2nd ed., American Chemical Society, Washington, D.C., 1960.

Sax, N.I., *Dangerous Properties of Industrial Materials*, 2nd ed., Reinhold, New York, 1963.

Thorpe, J. F., *Dictionary of Applied Chemistry*, 4th ed., Longmans, Green, New York, 1938–1957.

The Encyclopedia of Organic Chemistry, Elsevier, Amsterdam, 1946 (deals with complex organic compounds).

The Merck Index, 7th ed., Merck and Company, Rahway, N.J., 1960 (revised periodically).

I-4 REVIEWS AND ARTICLES

- Chemical Reviews**, American Chemical Society.
Quarterly Reviews (London), Chemical Society.
Annual Review of Biochemistry, Annual Reviews.
Journal of Chemical Education, Division of Chemical Education, American Chemical Society.

I-5 GENERAL ORGANIC TEXTBOOKS

- Fieser, L. F., and M. Fieser, *Advanced Organic Chemistry*, Reinhold, New York, 1961.
 Fieser, L. F., and M. Fieser, *Topics in Organic Chemistry*, Reinhold, New York, 1963.
 Gilman, H., *Organic Chemistry, an Advanced Treatise*, Wiley, New York, 1941-1953 (a variety of special topics).
 Hückel, W., *Theoretical Principles of Organic Chemistry* (English translation by Rathman), Elsevier, Amsterdam, 1955.
 Karrer, P., *Organic Chemistry*, Elsevier, Amsterdam, 1950.
 Noller, C. R., *Chemistry of Organic Compounds*, 3rd ed., Saunders, Philadelphia, 1965.
 Roberts, J. D., and M. Caserio, *Basic Principles of Organic Chemistry*, Benjamin, New York, 1965.
 Rodd, E. H., *Chemistry of Carbon Compounds*, Elsevier, Amsterdam, 1952-1965 (a comprehensive treatise).
 Royals, E. E., *Advanced Organic Chemistry*, Prentice-Hall, Englewood Cliffs, N.J. (study of organic reactions).
 Wheland, G. W., *Advanced Organic Chemistry*, 3rd ed., Wiley, New York, 1960 (structural development and reaction mechanisms).

I-6 REACTION MECHANISMS

- Eliel, E. L., *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962.
 Gould, E. S., *Mechanism and Structure in Organic Chemistry*, Henry Holt, New York, 1959.
 Hammett, L. P., *Physical Organic Chemistry*, McGraw-Hill, New York, 1940.
 Hine, J., *Physical Organic Chemistry*, 2nd ed., McGraw-Hill, New York, 1962.
 Ingold, C. K., *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N.Y., 1953.
 Leffler, J. E., *The Reactive Intermediates of Organic Chemistry*, Interscience, New York, 1956.

- Leffler, J. E., and E. Grunwald, *Rates and Equilibria of Organic Reactions*, Wiley, New York, 1963.
- Newman, M. S., *Steric Effects in Organic Chemistry*, Wiley, New York, 1956.
- Steacie, E. W. R., *Atomic and Free Radical Reactions*, 2nd ed., Reinhold, New York, 1954.
- Walling, C., *Free Radicals in Solution*, Wiley, New York, 1957.
- Waters, W. A., *Physical Aspects of Organic Chemistry*, 5th ed., Van Nostrand, Princeton, N.J., 1954.

I-7 SYNTHETIC METHODS

- Adams, R., *Organic Reactions*, Wiley, New York, From 1942. (A new volume covering new reactions of interest is issued on the average of about every 2 years.)
- Gilman, H., A. H. Blatt, and E. C. Horning, *Organic Syntheses*, Wiley, New York, annual volumes.
- Gilman, H., A. H. Blatt, and E. C. Horning, *Organic Syntheses, Collective Volumes*, Wiley, New York, 1941-1955 (collection and revision of material in annual volumes).
- Müller, E., *Houben-Weyls Methoden der organischen Chemie*, Georg Thieme Verlag, Stuttgart, 1952-1965.
- Theilheimer, W., *Synthetic Methods of Organic Chemistry*, Vols. I-IV in German, Vols. V onward in English, S. Karger, Basle, Wiley, New York, 1946-present.
- Wagner, R. B., and H. D. Zook, *Synthetic Organic Chemistry*, Wiley, New York, 1953.

I-8 ORGANIC ANALYSIS

- Braude, E. A., and F. C. Nachod, *Determination of Organic Structures by Physical Methods*, Academic, New York, 1955.
- Shriner, R. L., R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 5th ed., Wiley, New York, 1964.
- Siggia, S., *Quantitative Analysis Via Functional Groups*, 2nd ed., Wiley, New York, 1954.
- Vogel, A. I., *Elementary Practical Organic Chemistry*, Part II, "Qualitative Organic Analysis," and Part III, "Quantitative Organic Analysis," Longmans, Green, New York, 1957-1958.

I-9 PHYSICAL PROPERTIES

- Bellamy, L. J., *Infra-Red Spectra of Complex Molecules*, 2nd ed., Wiley, New York, 1958.

- Biemann, K., *Mass Spectrometry*, McGraw-Hill, New York, 1962.
- Pake, G. E., *Paramagnetic Resonance*, Benjamin, New York, 1962.
- Roberts, J. D., *Nuclear Magnetic Resonance: Applications to Organic Chemistry*, McGraw-Hill, New York, 1959.
- Silverstein, R. M., and G. C. Bassler, *Spectrometric Identification of Organic Compounds*, Wiley, New York, 1963.

I-10 GENERAL LABORATORY PROCEDURES

- Weissberger, A., *Technique of Organic Chemistry*, Wiley, Interscience Division, New York, 1945-present.



Glossary and Index of Named Reactions

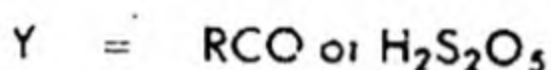
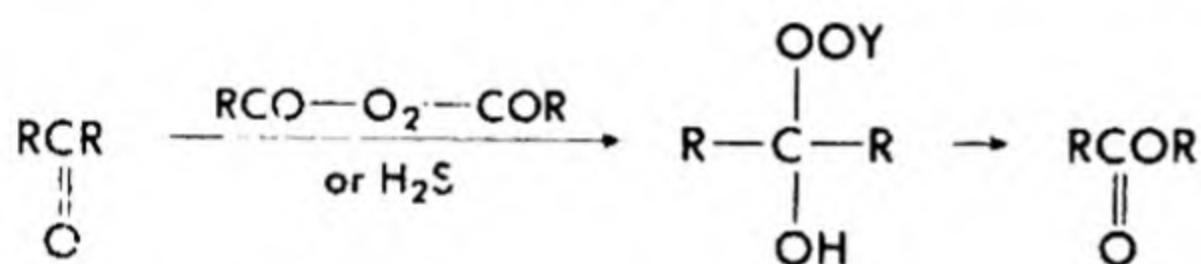
II-1 ARNDT-EISTERT REACTION

A method of preparing acids or their derivatives from acid derivatives of one less carbon atom (page 504):



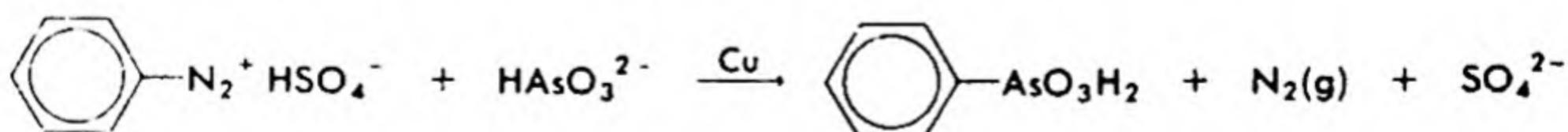
II-2 BAEYER-VILLIGER REACTION

The oxidative rearrangement of a ketone to an ester (pages 520-521):



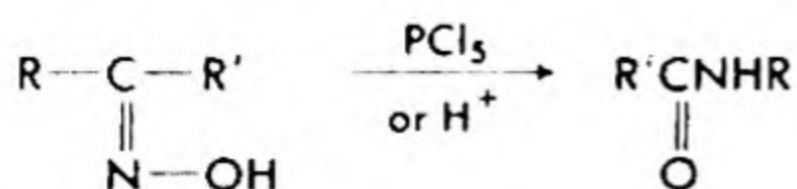
II-3 BART REACTION

Replacement of a diazonium group with an arsono group by the action of sodium arsenite and copper powder in neutral solution:



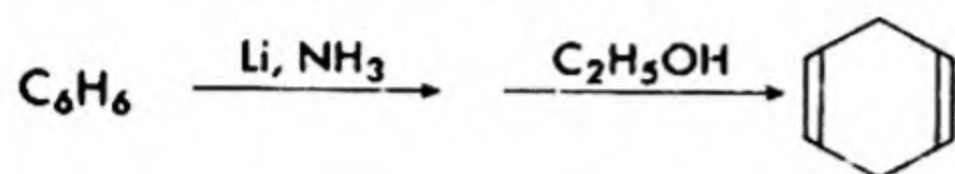
II-4 BECKMANN REARRANGEMENT

Rearrangement of oximes to amides (pages 516-519):



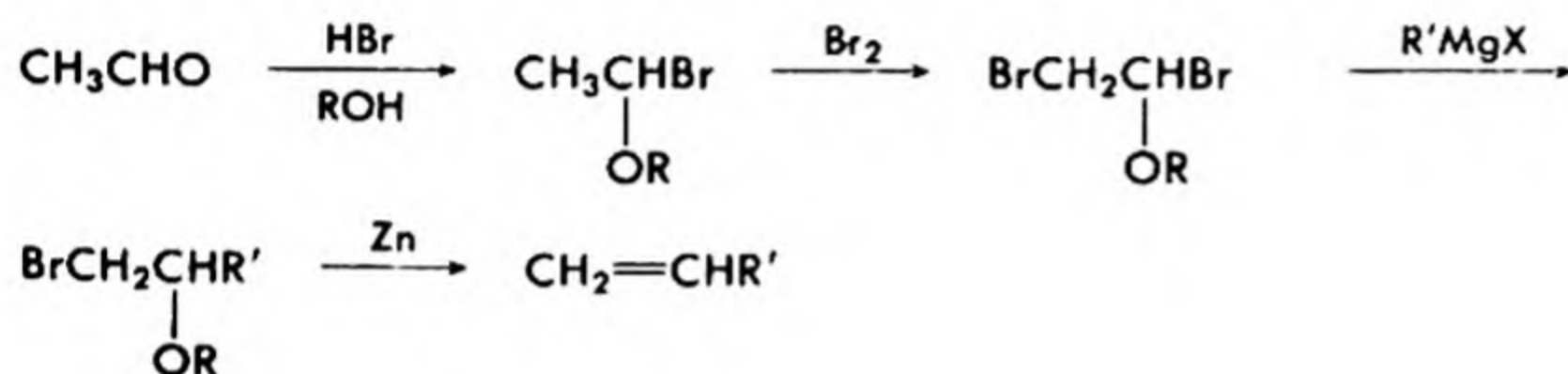
II-5 BIRCH REDUCTION

The use of ammonia solutions of alkali metals to give 1,4-dihydroarenes (pages 583–584):



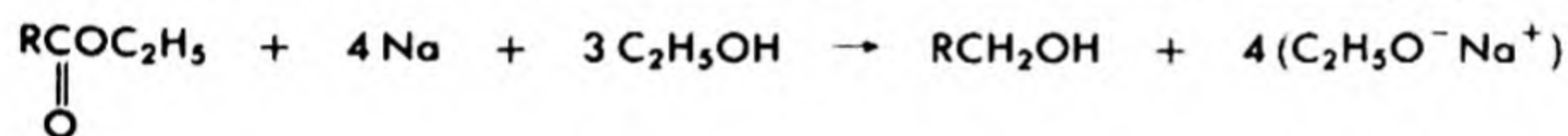
II-6 BOORD OLEFIN SYNTHESIS

A four-step synthesis of olefins involving removal of bromine and an alkoxy group by zinc in the last step (pages 433–434):



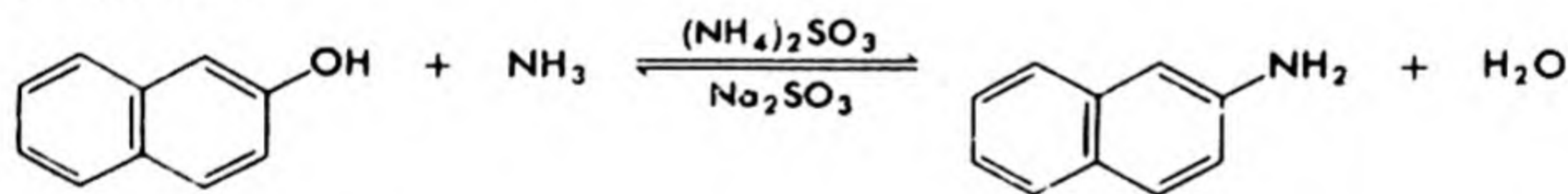
II-7 BOUVEAULT-BLANC REACTION

Reduction of an ester to an alcohol by metallic sodium (page 583):



II-8 BUCHERER REACTION

Ammonolysis of naphthols to prepare naphthylamines and the reverse (page 486):



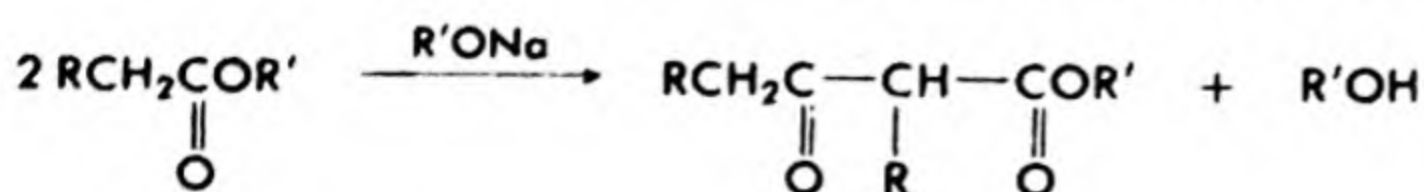
II-9 CANNIZZARO REACTION

Base-catalyzed oxidation-reduction of aldehydes (pages 488–489):



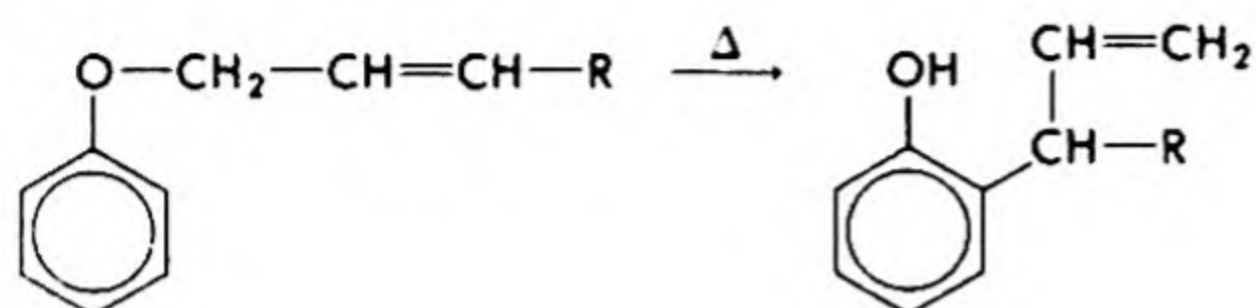
II-10 CLAISEN ESTER SYNTHESIS

Base-catalyzed condensation of esters to β -keto esters (pages 459–460):



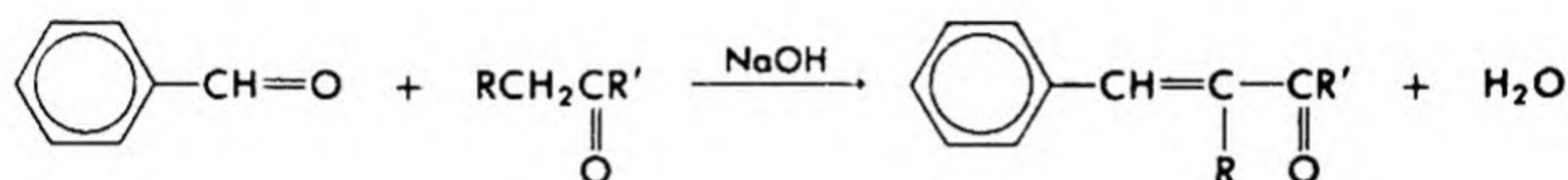
II-11 CLAISEN REARRANGEMENT

Rearrangement of allyl phenyl ethers to *o*-allyl phenols (pages 428–429):



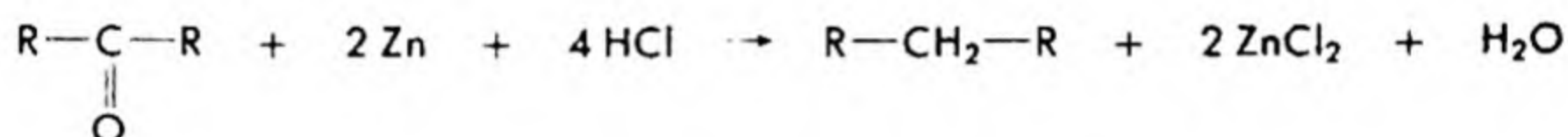
II-12 CLAISEN-SCHMIDT CONDENSATION

An aldol condensation between an aromatic aldehyde and a ketone with an active methylene group (page 458):



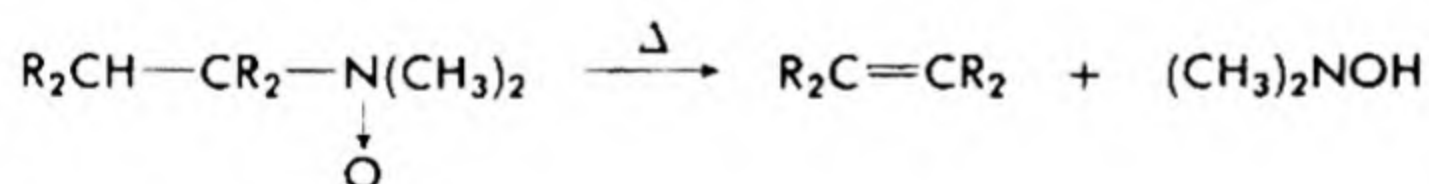
II-13 CLEMMENSON REDUCTION

Reduction of a keto group to a methylene group by amalgamated zinc and acid (page 582):



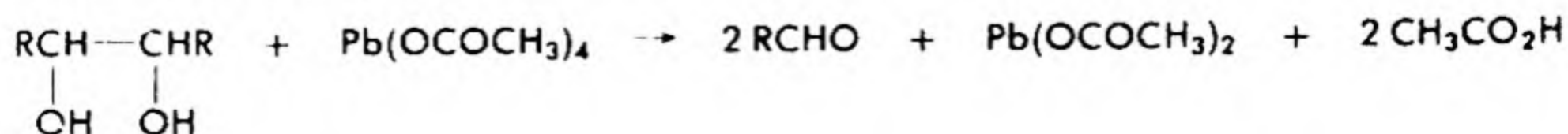
II-14 COPE ELIMINATION

Pyrolysis of an amine oxide to an olefin (page 304):



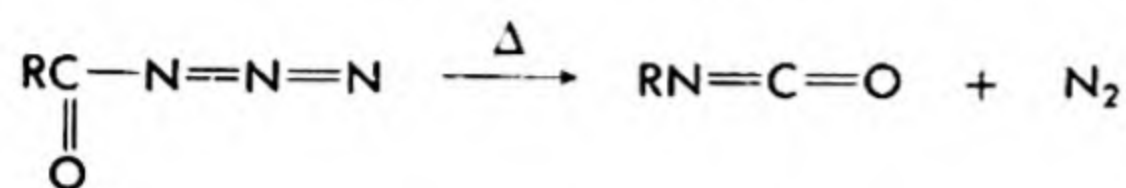
II-15 CRIEGEE REACTION

Oxidation of vicinal diols or α -hydroxyketones with lead tetraacetate to form aldehydes (pages 562–564):



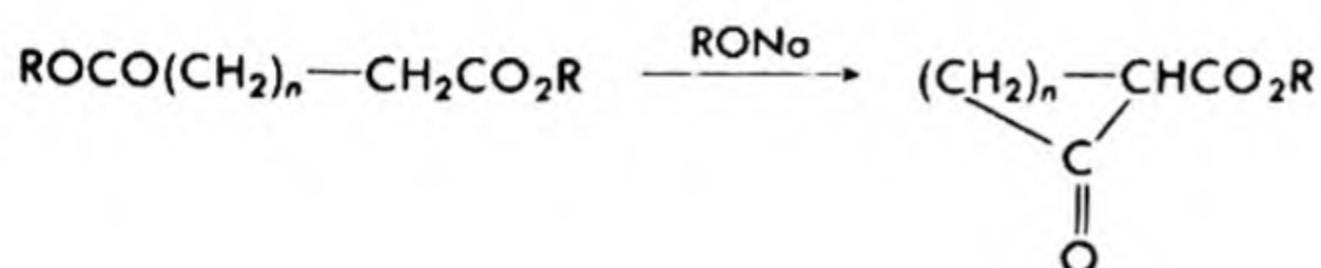
II-16 CURTIUS REARRANGEMENT

Rearrangement of an acid azide to an isocyanate, similar to the Hofmann rearrangement of amides (pages 311–312, 514–516):



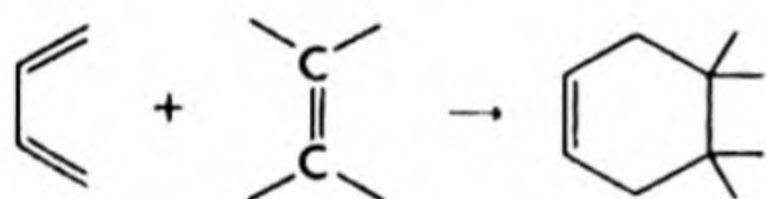
II-17 DIECKMANN REACTION

An internal Claisen ester condensation resulting in a cyclic ketone (page 460):



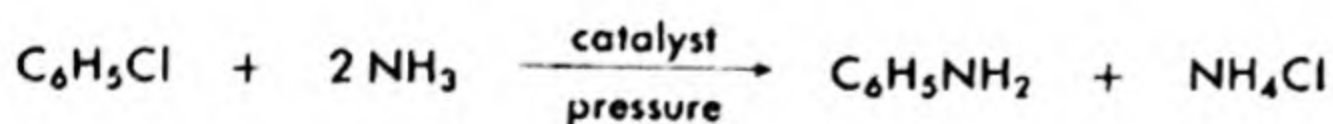
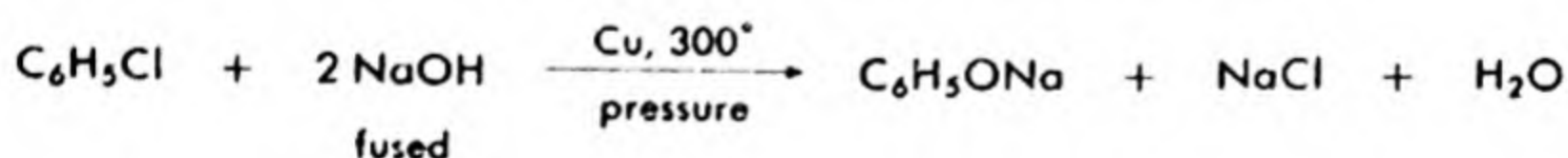
II-18 DIELS-ALDER REACTION

Diene synthesis—a condensation of a conjugated diene with an unsaturated compound (pages 588–593):



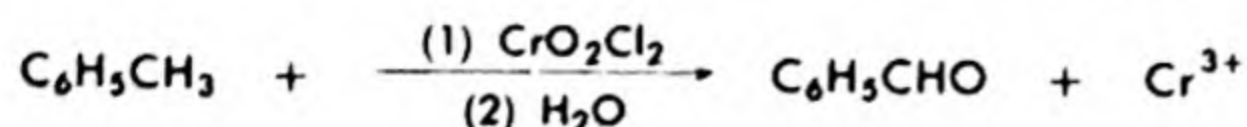
II-19 DOW PROCESS

Either of two processes developed by Dow Chemical Co. to replace an aromatic halogen, producing a phenoxide or an amine:



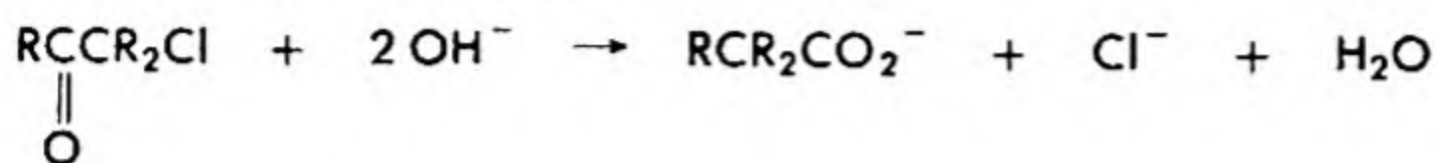
II-20 ÉTARD PROCESS

Oxidation of toluene to benzaldehyde by chromyl chloride (page 560):



II-21 FAVORSKY REARRANGEMENT

Alkaline hydrolysis and rearrangement of α -chloroketones to salts of carboxylic acids (pages 522–523):

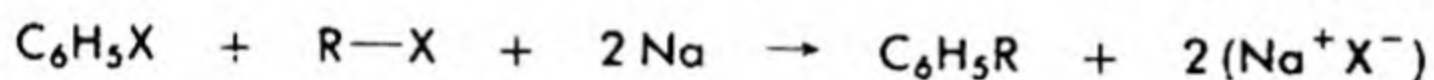


11-22 FISCHER-TROPSCH PROCESS

A means of treating mixtures of carbon monoxide and hydrogen so that alcohols or alkanes are produced.

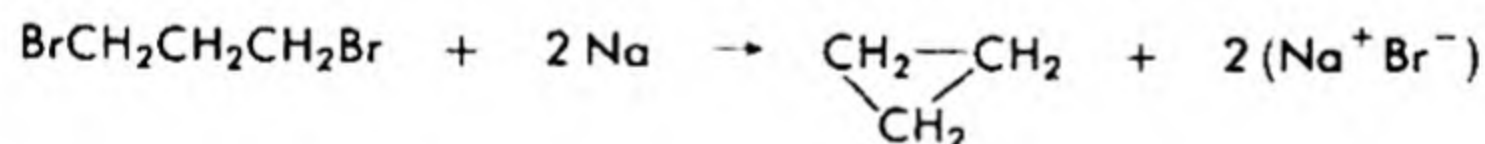
II-23 FITTIG REACTION (WURTZ-FITTIG REACTION)

Coupling of an aromatic group and an aliphatic group by treating a mixture of the appropriate halides with sodium (page 434):



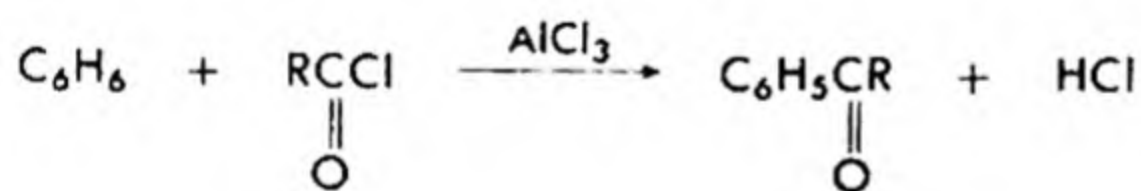
II-24 FREUND REACTION

A cyclization involving an internal Wurtz reaction:



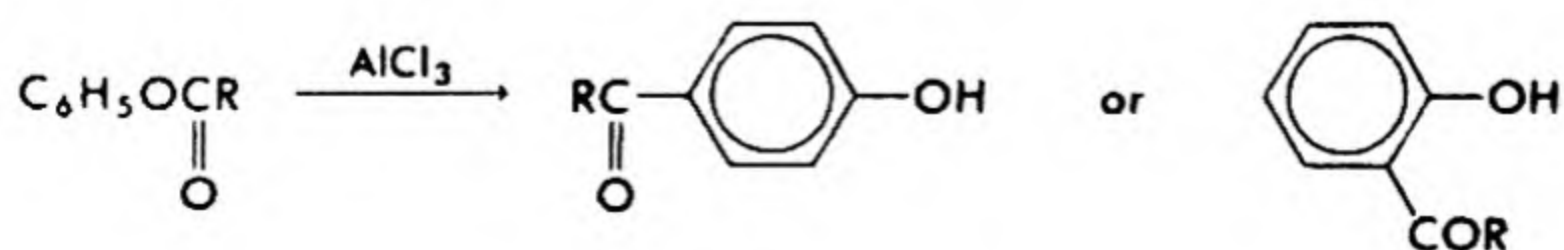
11-25 FRIEDEL-CRAFTS REACTION

Alkylation or acylation of aromatic hydrocarbons through the agency of aluminum chloride, boron trifluoride, antimony pentachloride, stannic chloride, or zinc chloride (pages 338, 344-347, 361-362):



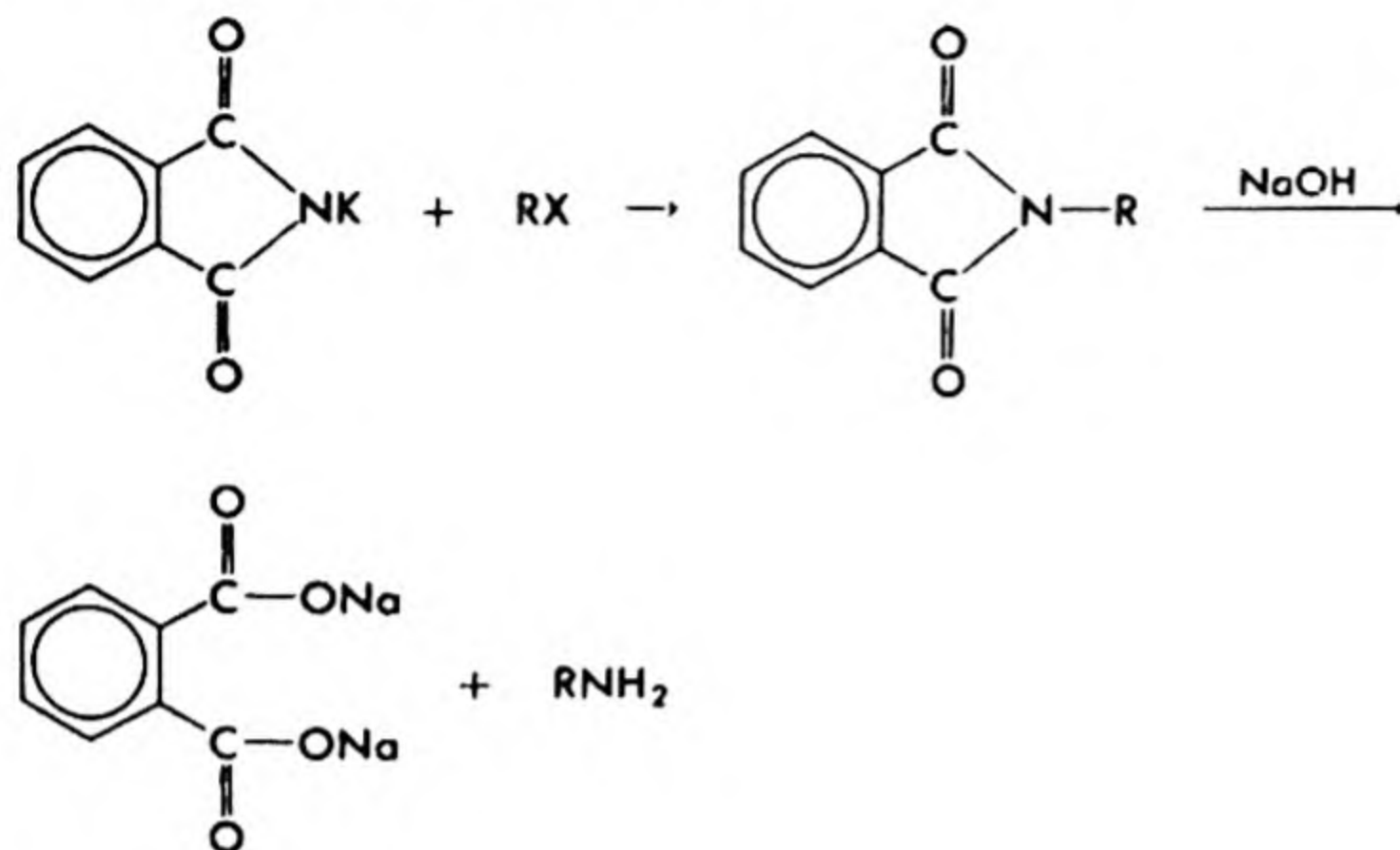
11-26 FRIES REARRANGEMENT

Lewis-acid catalyzed rearrangement of a phenyl ester to a phenolic ketone (page 528):



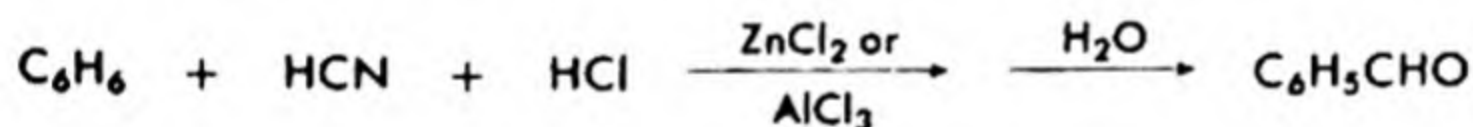
II-27 GABRIEL SYNTHESIS

A method for preparing pure primary amines. Two valences of the nitrogen atom are occupied in an imide linkage, leaving only one position free for alkylation (page 278):



II-28 GATTERMANN ALDEHYDE SYNTHESIS

Formylation of an aromatic ring with hydrogen cyanide:



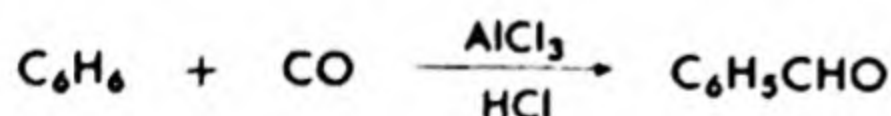
II-29 GATTERMANN DIAZO REACTION

Modification of the Sandmeyer reaction which uses the acid and copper powder instead of the cuprous salt (pages 499–500):



II-30 GATTERMANN-KOCH REACTION

Formylation of an aromatic ring with carbon monoxide:



II-31 GRIGNARD REACTION

Preparation of an organomagnesium halide in dry ether (pages 422–423):

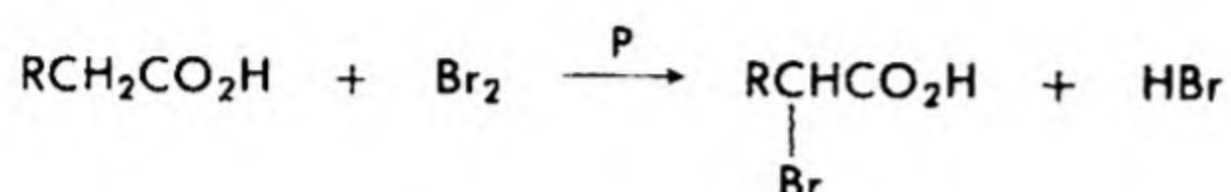


II-32 GRIGNARD SYNTHESIS

Use of the Grignard Reagent, RMgX , in any of a variety of syntheses. Also called Grignard reaction in Europe (pages 436-441).

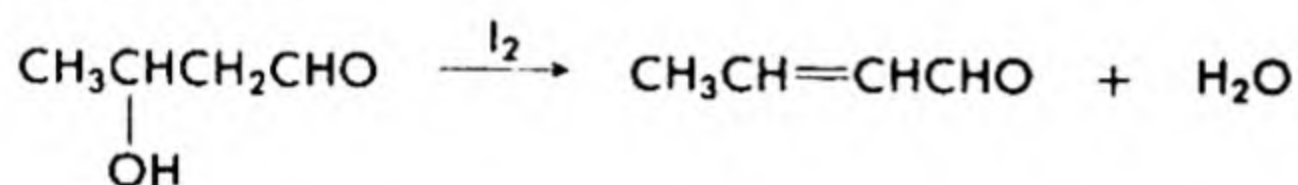
II-33 HELL-VOLHARD-ZELINSKY REACTION

A method for halogenating aliphatic acids in the alpha position (page 451):



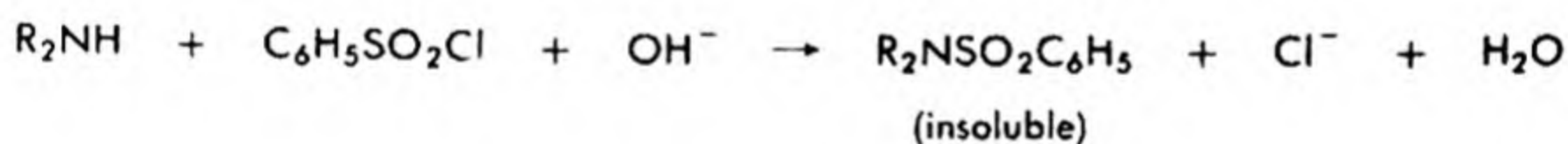
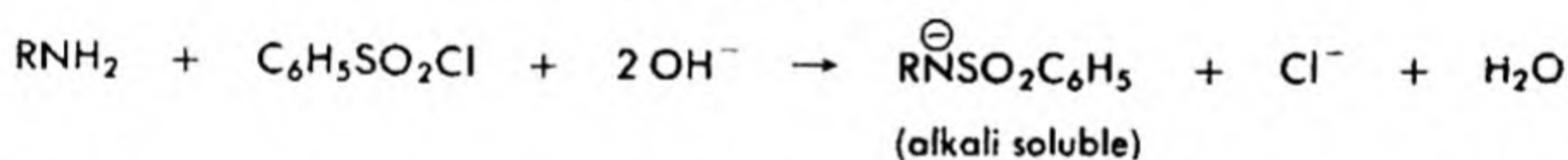
II-34 HIBBERT METHOD

Dehydration of β -hydroxy carbonyl compounds by the use of iodine as a catalyst:



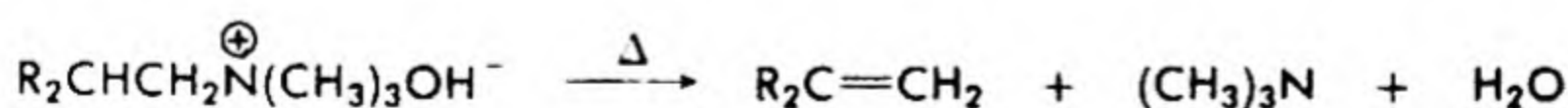
II-35 HINSBERG REACTION

A method of classifying or separating amines by difference of behavior with benzenesulfonyl chloride (page 389):



II-36 HOFMANN ELIMINATION

A method of eliminating amino nitrogen by the formation of quaternary ammonium hydroxides and their thermal decomposition (pages 301-303):



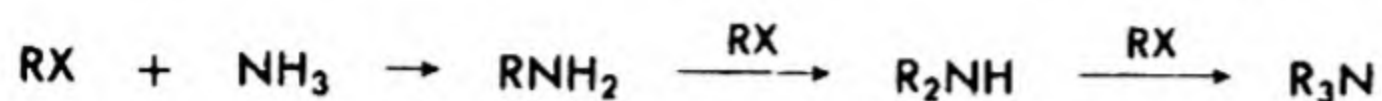
II-37 HOFMANN REARRANGEMENT

Formation of amines or, with special conditions, isocyanates, from amides with shortening of the carbon chain by one atom by treatment with halogen and alkali (pages 311, 514-516):



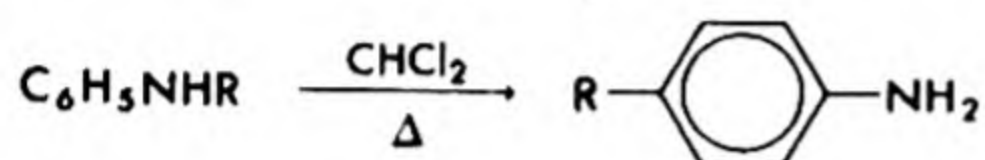
II-38 HOFMANN SYNTHESIS OF AMINES

Reaction of alkyl halides with ammonia (page 278):



II-39 HOFMANN-MARTIUS REARRANGEMENT

Rearrangement of aromatic secondary amines similar to the benzidine rearrangement and with similar mechanism:



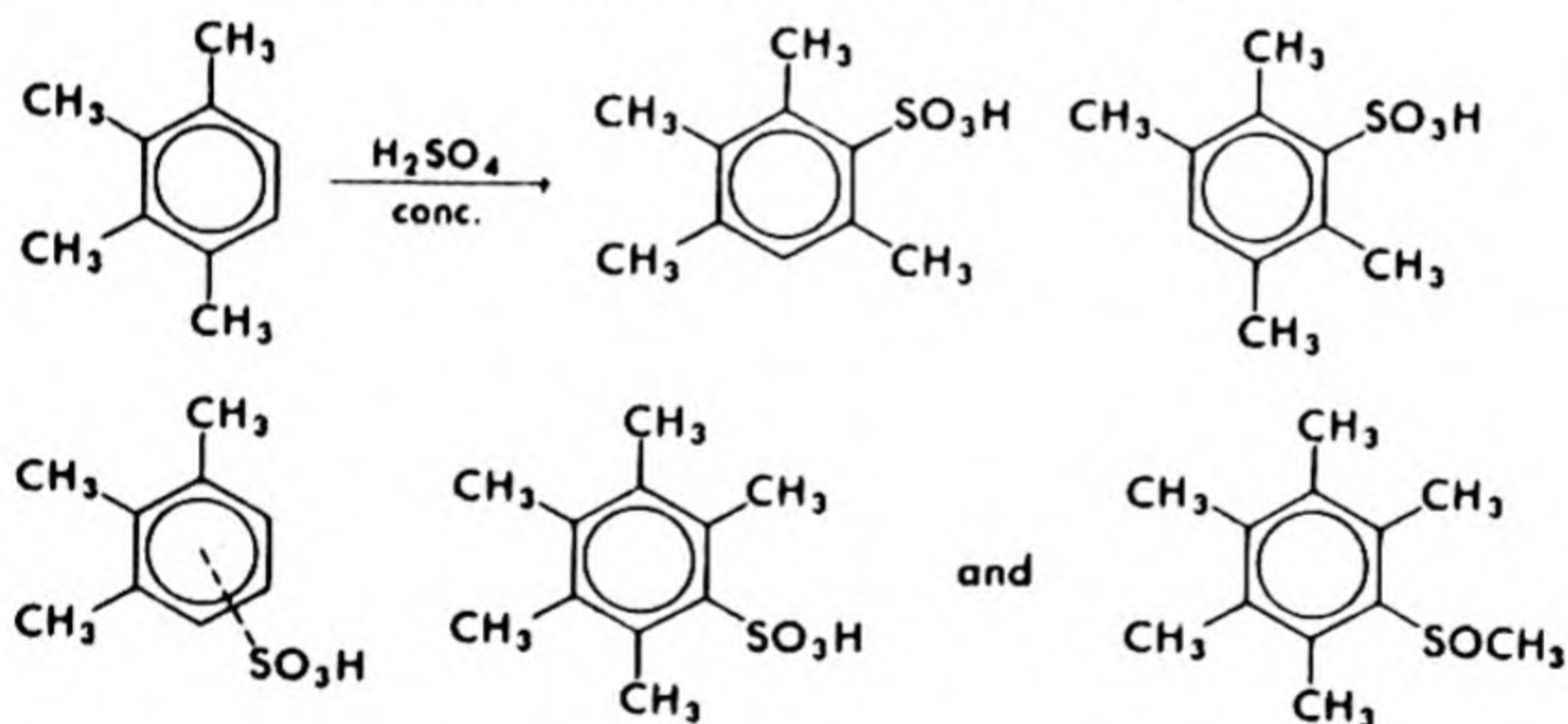
II-40 HUNSDIECKER REACTION

Preparation of alkyl chlorides or alkyl bromides by treatment of silver alkanoates with free halogen (also called Borodine-Hunsdiecker Reaction):



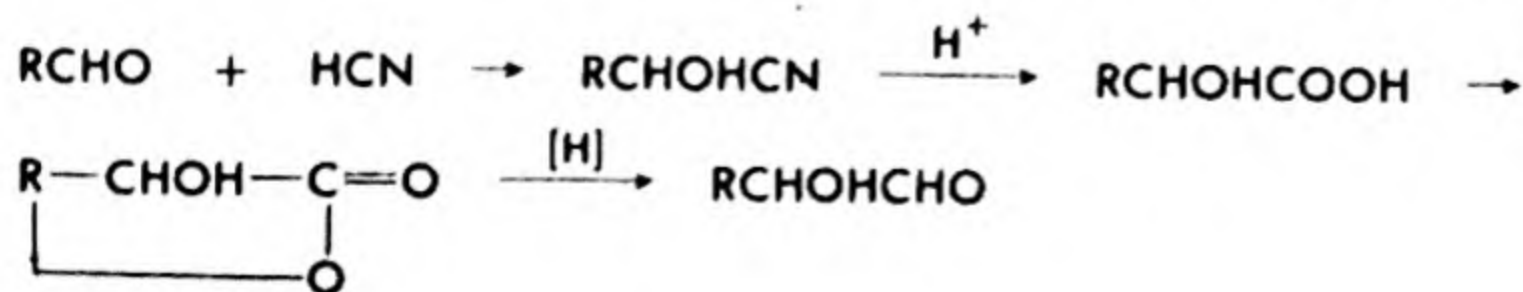
II-41 JACOBSEN REARRANGEMENT

Rearrangement and transmigration of alkyl groups on highly alkylated arenes by treatment with sulfuric acid (pages 523-525):



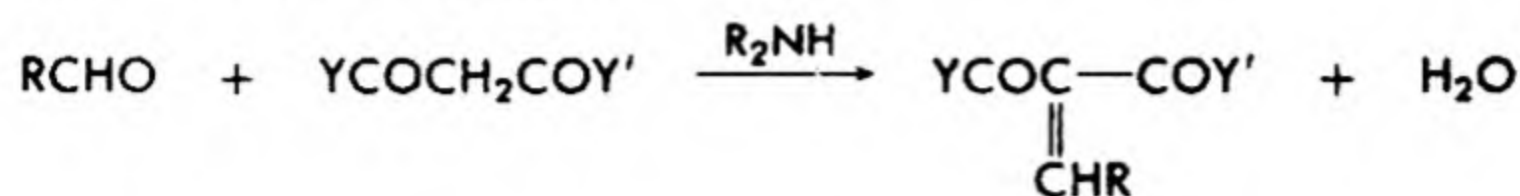
II-42 KILIANI-FISCHER SYNTHESIS

A method for lengthening the carbon chain in aldose series (page 699):



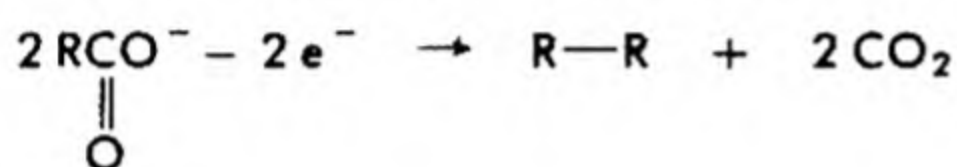
II-43 KNOEVENAGEL REACTION

A type of condensation involving the use of a secondary amine as the basic condensing agent:



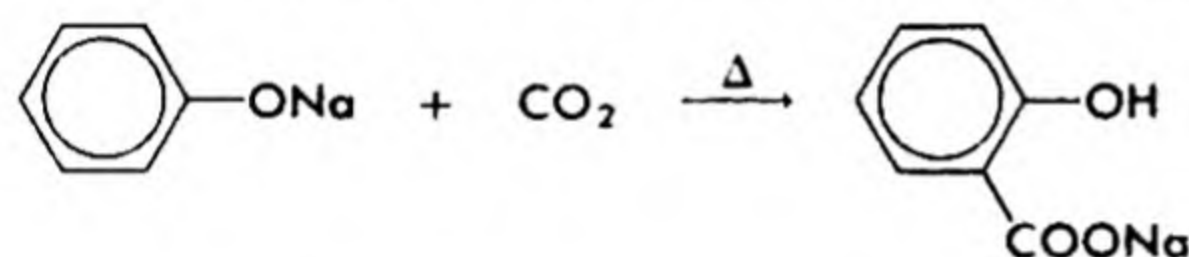
II-44 KOLBE ELECTROLYTIC SYNTHESIS

Preparation of symmetrical alkanes by electrolysis of alkali metal salts of carboxylic acids (page 543):



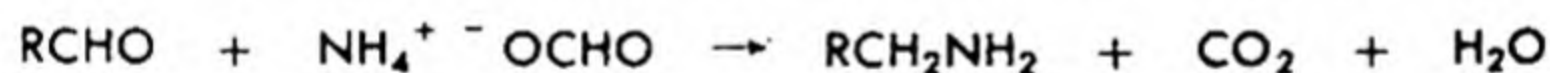
II-45 KOLBE-SCHMITT SYNTHESIS

Preparation of *o*-carboxyphenols from phenols:



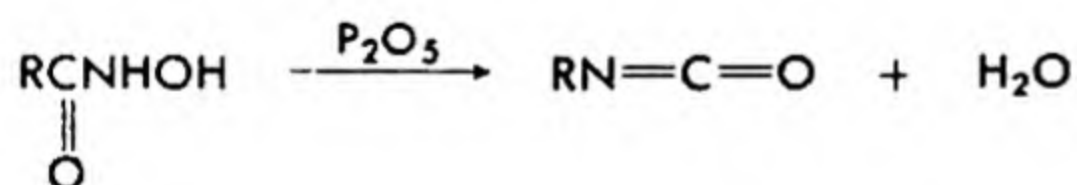
II-46 LEUCKART REACTION

An oxidation-reduction reaction similar to the crossed Cannizzaro reaction in which an aldehyde is converted to a primary amine:



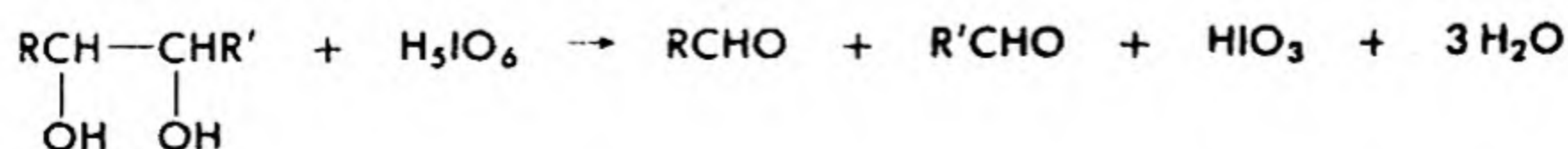
II-47 LOSSEN REARRANGEMENT

A rearrangement of hydroxylamides similar to the Curtius and Hofmann rearrangements (pages 514–516):



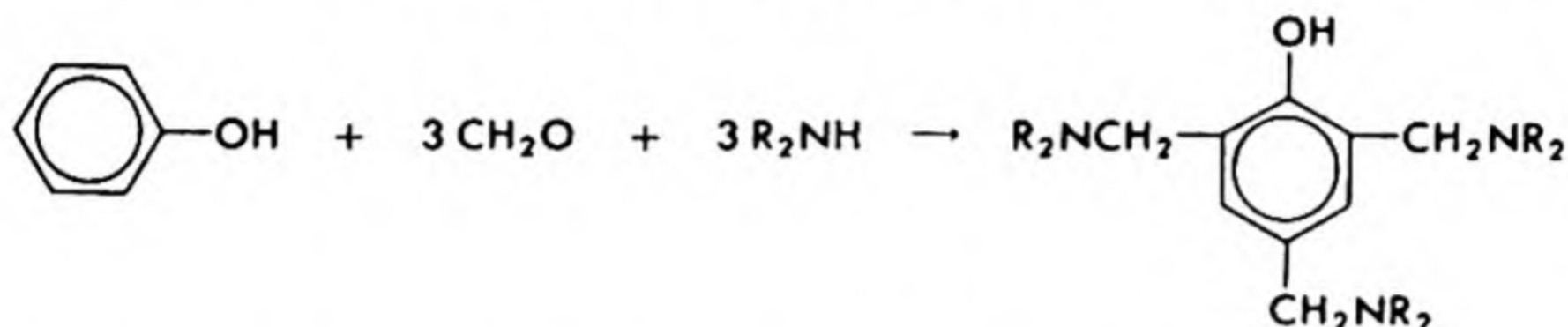
II-48 MALAPRADE REACTION

An oxidation suitable for distinguishing vicinal dihydroxy compounds or for cleaving such compounds to aldehydes and ketones (page 562):



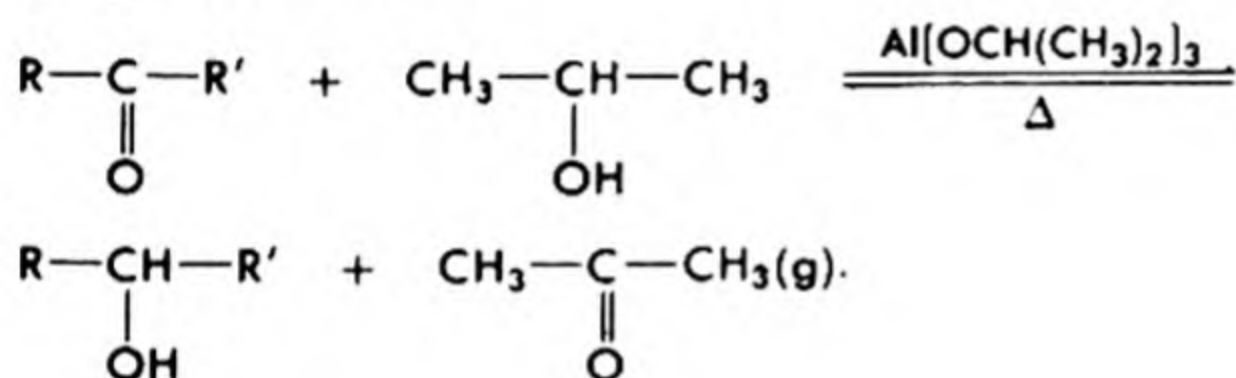
II-49 MANNICH REACTION

Replacement of active hydrogen atoms in organic compounds by aminomethyl groups through the reaction of amines and formaldehyde:



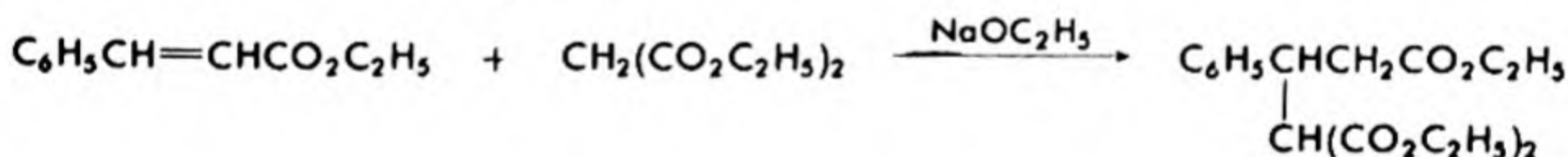
II-50 MEERWEIN-PONNDORF-VERLEY REACTION

A base-catalyzed equilibrium between two alcohols and the corresponding carbonyl compounds which is driven to completion by the continuous removal of the most volatile component, usually acetone, by distillation (pages 490-492):



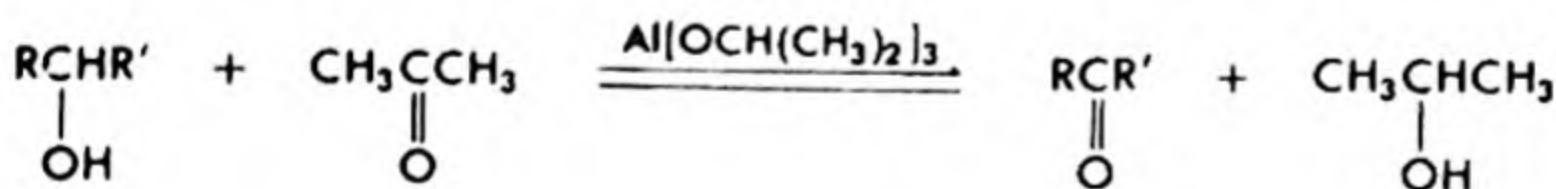
II-51 MICHAEL REACTION

Addition of active methylene compounds to α,β -unsaturated esters, ketones, or nitriles (pages 476-477):



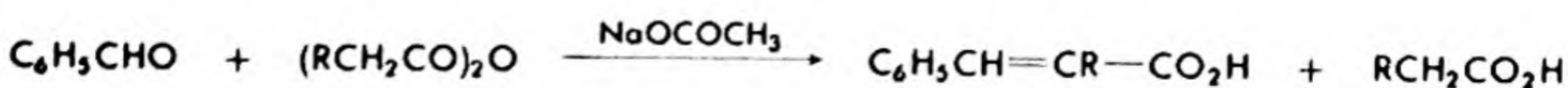
II-52 OPPENAUER OXIDATION

The reverse of the Meerwein-Ponndorf reaction, driven to completion by a large excess of acetone (or other ketone) (pages 491-492):



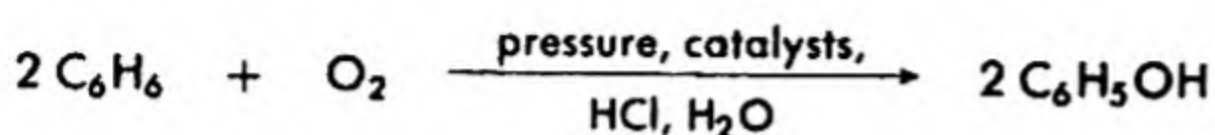
II-53 PERKIN CONDENSATION

Condensation of an aromatic aldehyde with an acid anhydride by the use of sodium acetate as the catalyst (pages 458-459):



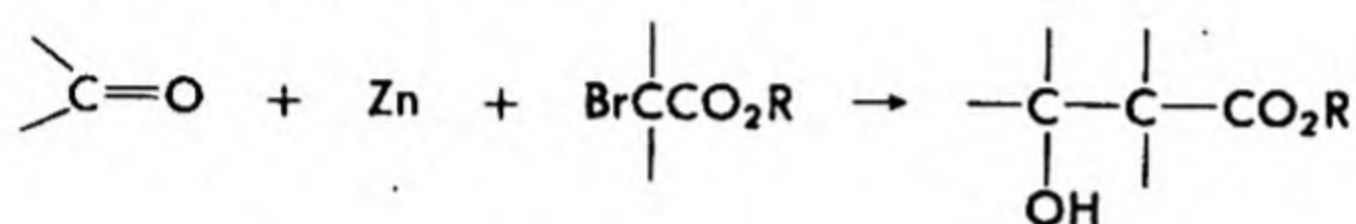
II-54 RASCHIG PROCESS

A method for the manufacture of phenol:



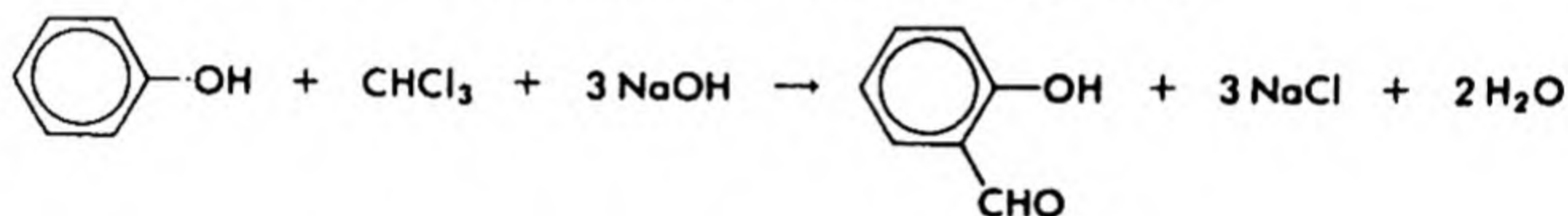
II-55 REFORMATZSKY REACTION

Reaction of carbonyl compounds with α -haloesters and zinc to give β -hydroxy esters (page 438):



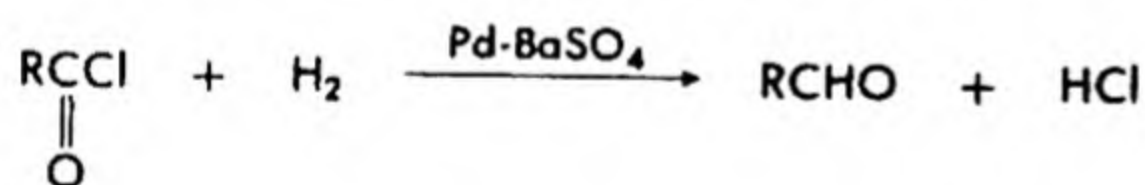
II-56 REIMER-TIEMANN REACTION

Formylation of a phenol with chloroform (page 367):



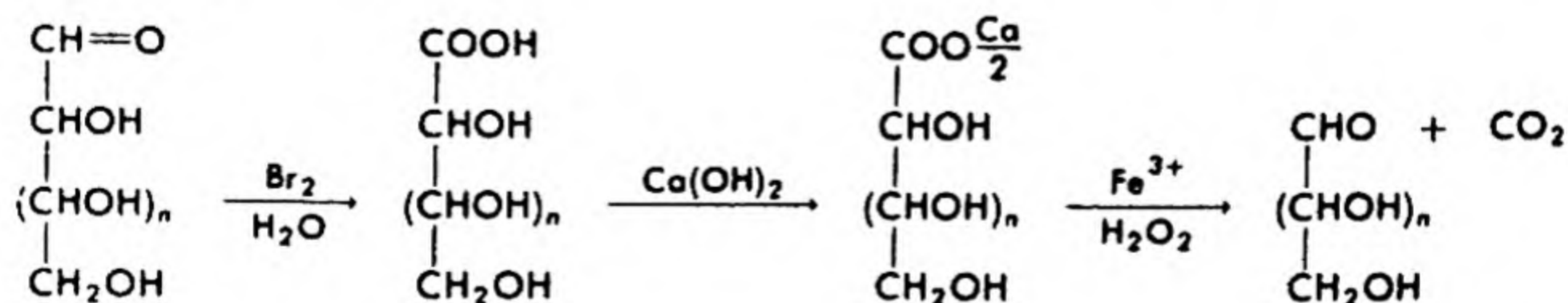
II-57 ROSENMUND REDUCTION

The catalytic reduction of an acid halide to an aldehyde (page 577):



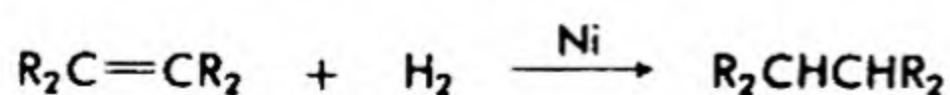
II-58 RUFF DEGRADATION

A method of degrading aldoses to the aldoses of one less carbon atom (page 699):



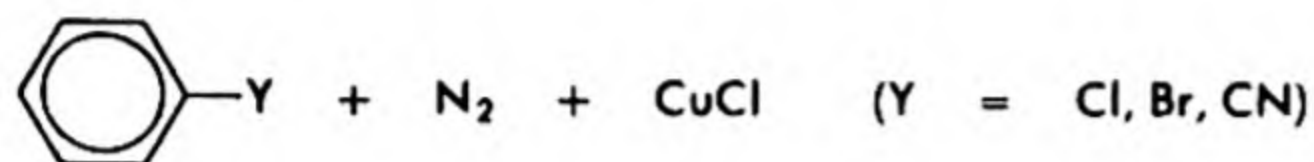
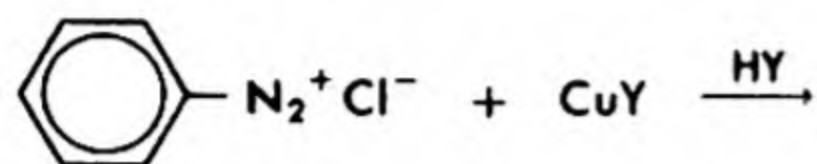
II-59 SABATIER-SENDRENS REACTION

Hydrogenation of carbon-carbon double bonds in the presence of nickel catalyst (page 575):



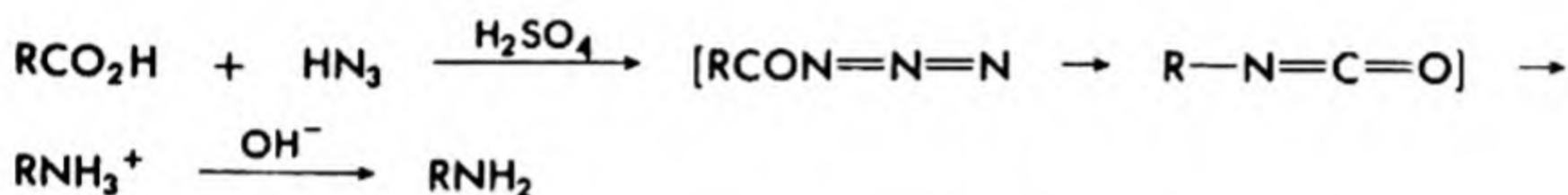
II-60 SANDMEYER REACTIONS

The replacement of a diazonium group through the agency of a cuprous salt (page 499):



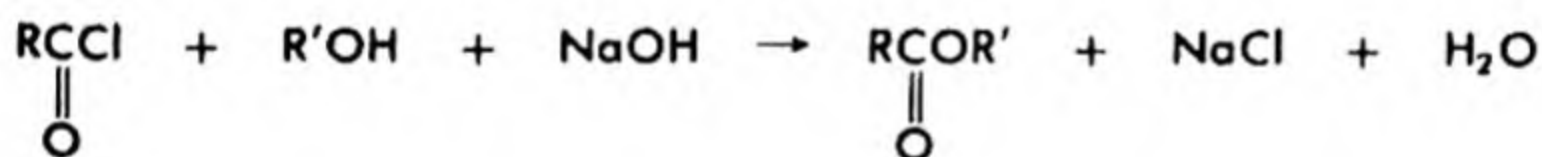
II-61 SCHMIDT REARRANGEMENT

Conversion of a carboxylic acid to an amine one carbon atom shorter by treatment with hydrazoic acid; similar to Curtius rearrangement (pages 311-312, 514-516):



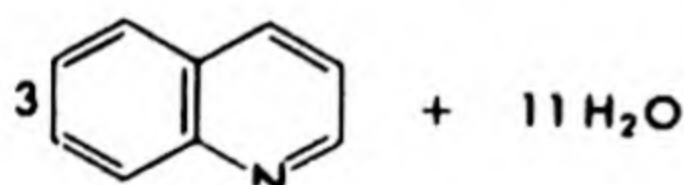
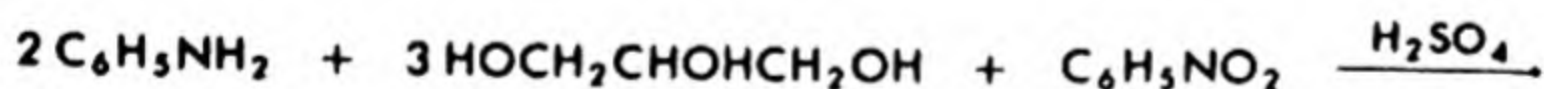
II-62 SCHOTTEN-BAUMANN REACTION

Acylation of an alcohol, phenol, or amine with an acyl halide or anhydride in alkaline solution (page 381):



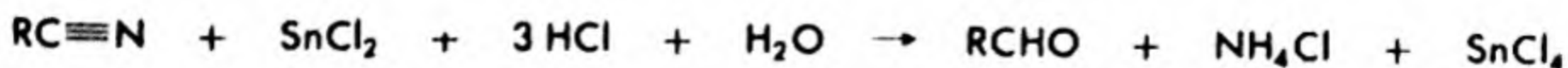
II-63 SKRAUP SYNTHESIS

A method for preparing quinoline:



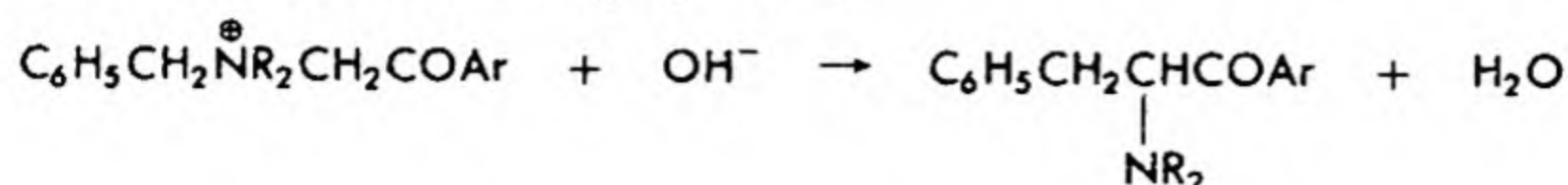
II-64 STEPHEN REDUCTION

Reduction of a nitrile to an aldehyde by the use of stannous chloride (page 585):



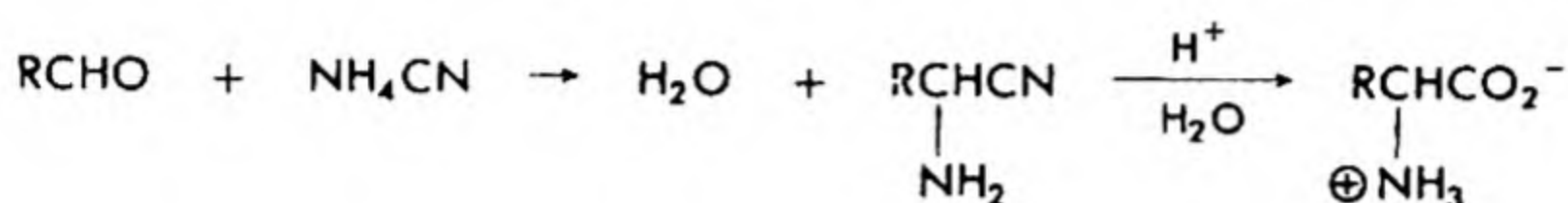
II-65 STEVENS REARRANGEMENT

Alkaline rearrangement of benzyldialkylammoniomethyl ketones to α -dialkylamino ketones (page 523):



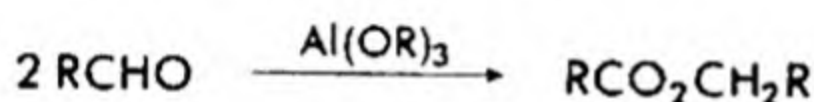
II-66 STRECKER SYNTHESIS

A method for the preparation of amino acids from aldehydes:



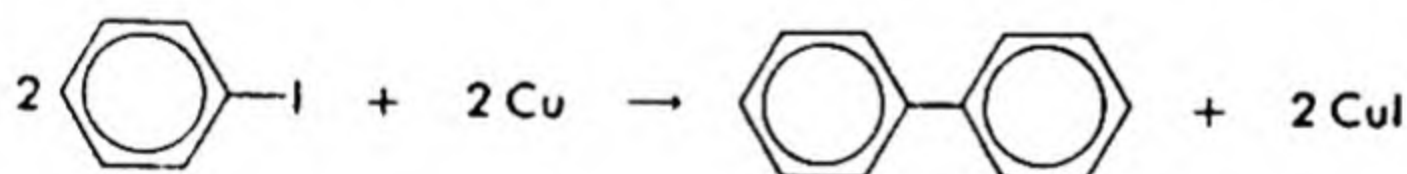
II-67 TISHCHENKO REACTION

Conversion of 2 moles of aldehyde into an ester using an anhydrous metal alkoxide (page 490):



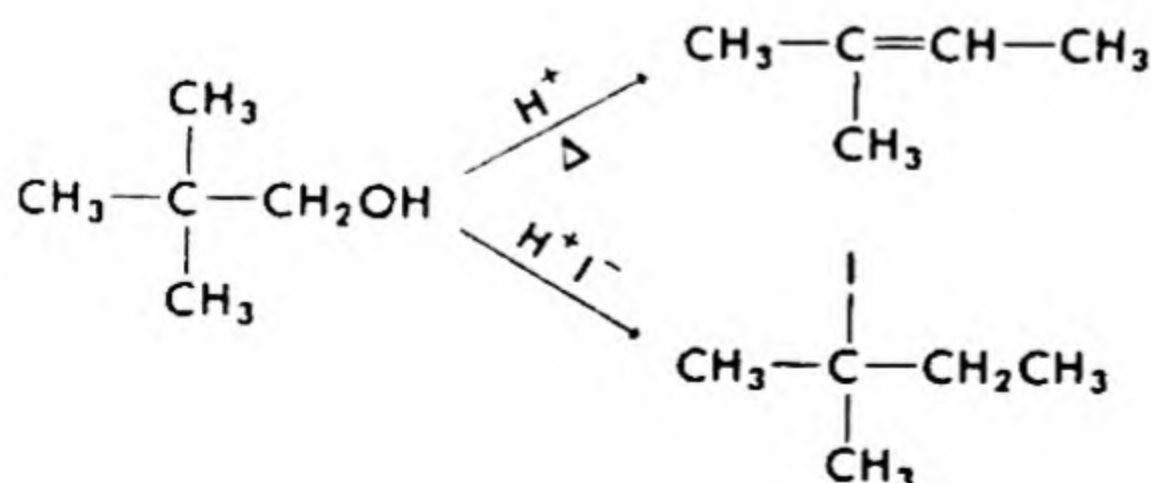
II-68 ULLMANN REACTION

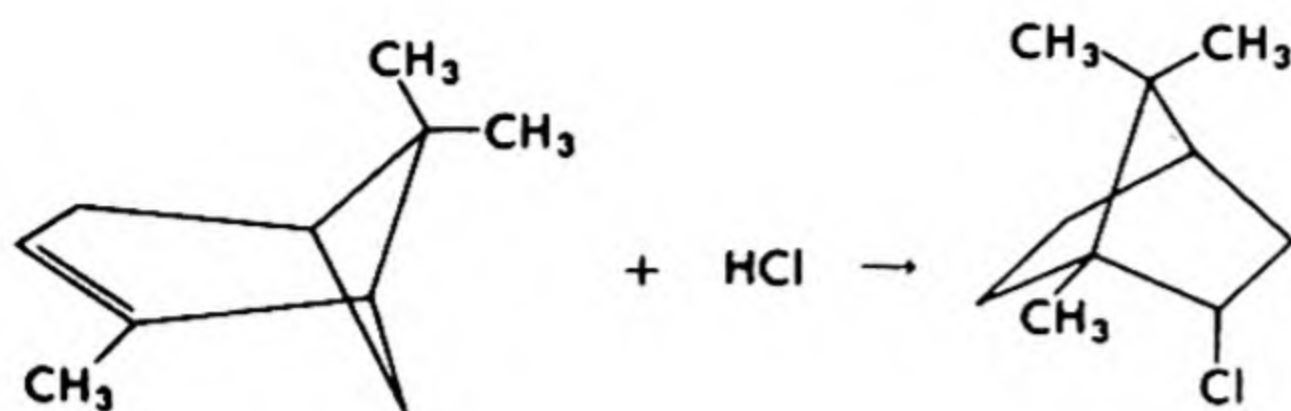
Synthesis of biaryls by coupling of aryl iodides with powdered copper:



II-69 WAGNER-MEERWEIN REARRANGEMENT

Any of several carbonium-ion rearrangements involving 1,2-migrations of alkyl groups, so as to give products with rearranged carbon skeletons. May occur in displacements, additions, or eliminations (pages 287–289, 511–514):





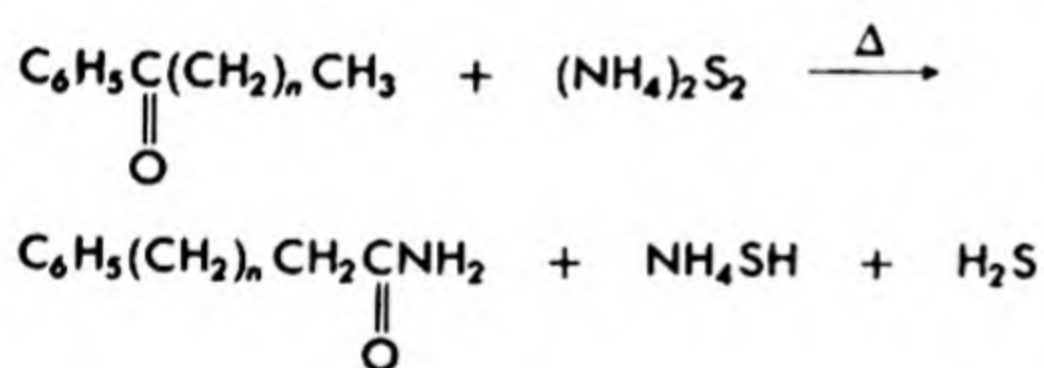
II-70 WALDEN INVERSION

Inversion of configuration about a carbon atom in a displacement reaction; a characteristic of the direct displacement mechanism (pages 262–263, 629–631):



II-71 WILLGERODT REACTION

A method for producing aromatic acid derivatives with the carboxyl group at the end of a side chain (pages 529–530):



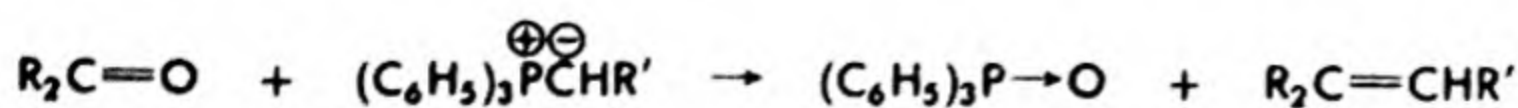
II-72 WILLIAMSON SYNTHESIS

The preparation of ethers from an alkoxide and a halide (pages 277–278):



II-73 WITTIG SYNTHESIS

The preparation of olefins from carbonyl compounds and triphenylphosphine ylides (pages 428–430):



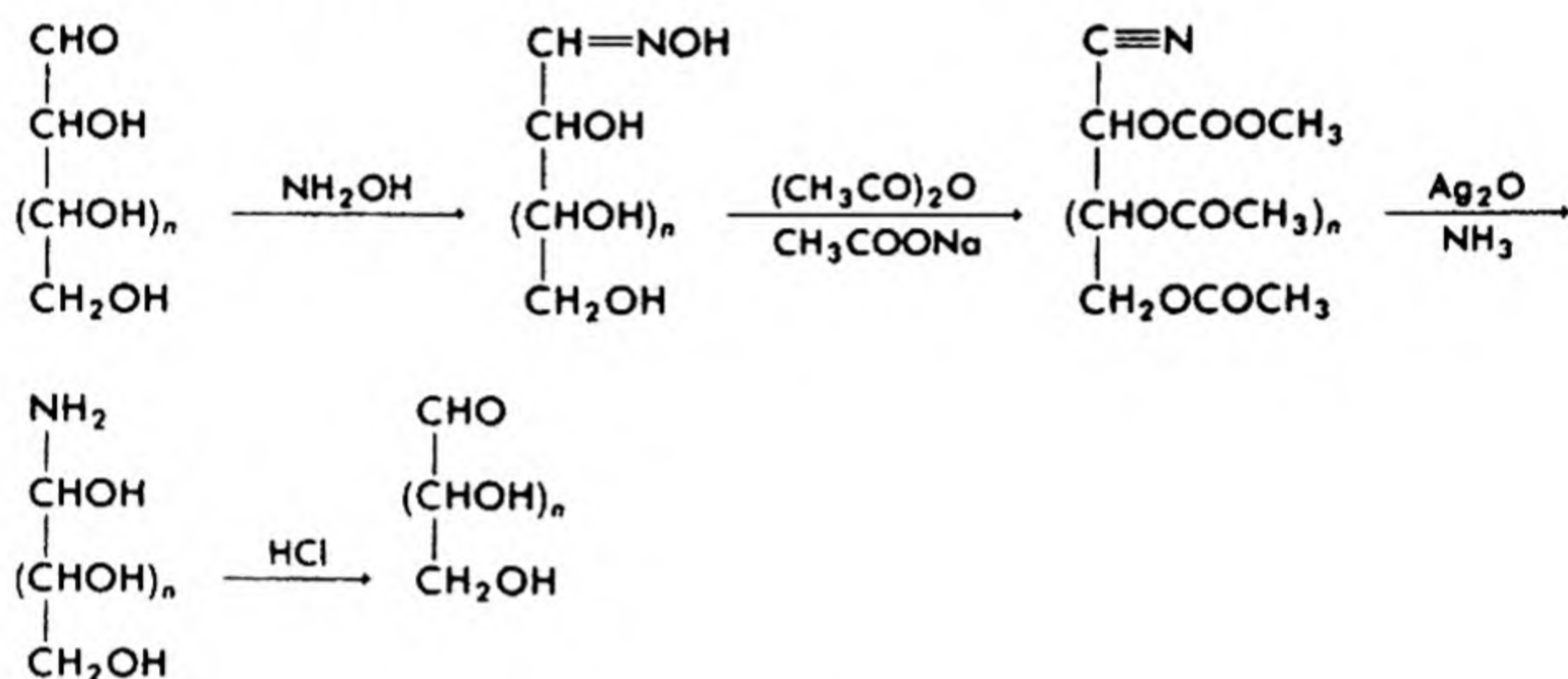
II-74 WÖHLER SYNTHESIS

The preparation of urea from an ammonium salt and a cyanate (page 411):



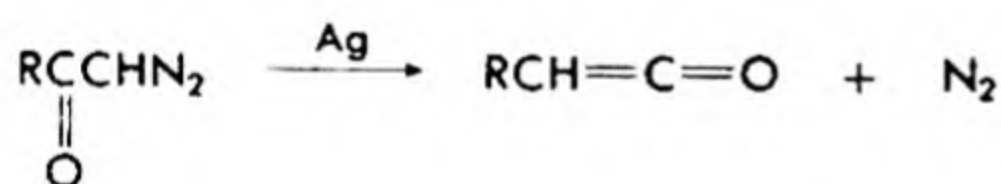
II-75 WOHL DEGRADATION

A reversal of the cyanhydrin synthesis applied to the degradation of aldoses (page 699):



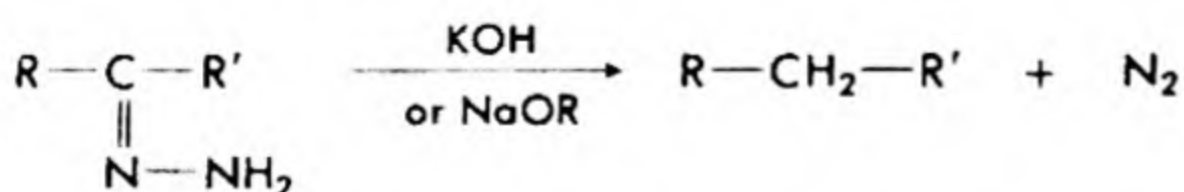
II-76 WOLFF REARRANGEMENT

The diazoketone rearrangement step in the Arndt-Eistert synthesis (page 504):



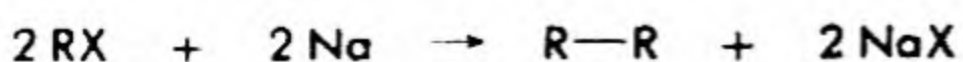
II-77 WOLFF-KISHNER REDUCTION

Reduction of a keto group to a methylene group by way of the hydrazone (pages 505-507):



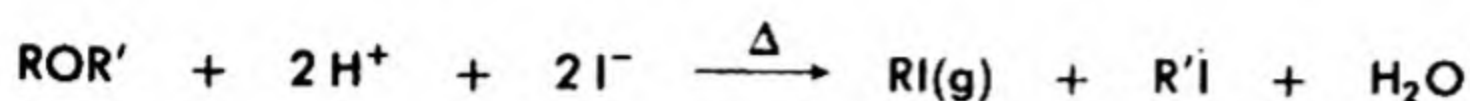
II-78 WURTZ REACTION

Coupling of alkyl halides with sodium (pages 434, 532):



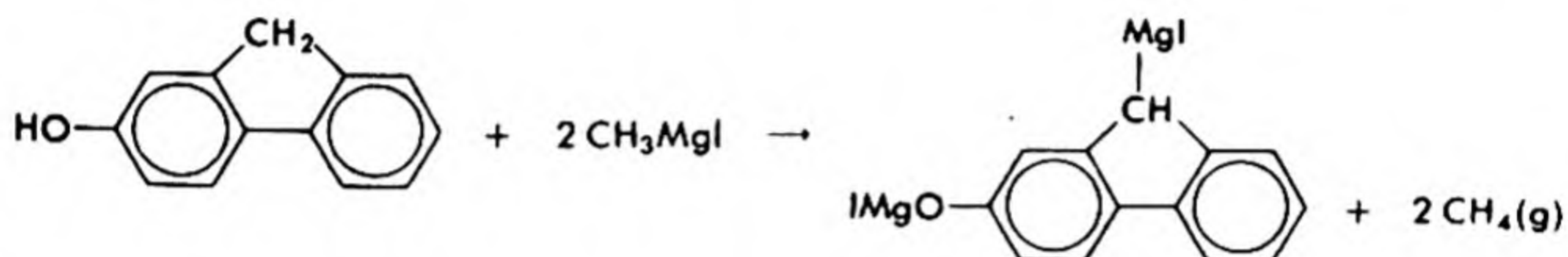
II-79 ZEISEL METHOXYL DETERMINATION

A technique for ascertaining the presence of methoxyl or ethoxyl groups in ethers by treatment of the ethers with hydriodic acid (page 285):



II-80 ZEREVITINOFF METHOD FOR ACTIVE HYDROGEN

Treatment of a compound with methylmagnesium iodide to determine the equivalents of replaceable (acidic) hydrogen (also Chugaev-Zerevitinoff method):



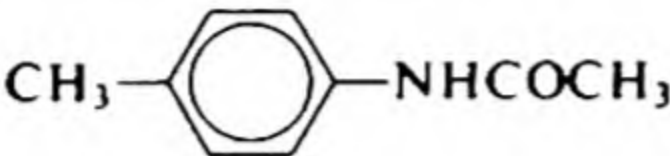
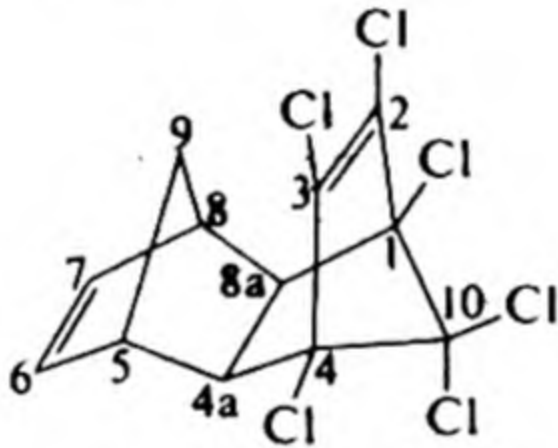

The volume of evolved methane is measured.

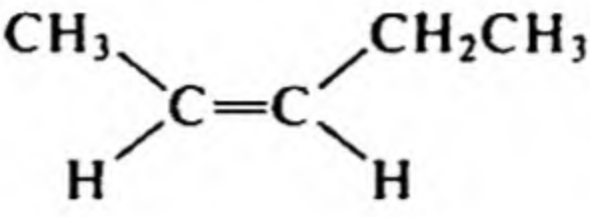
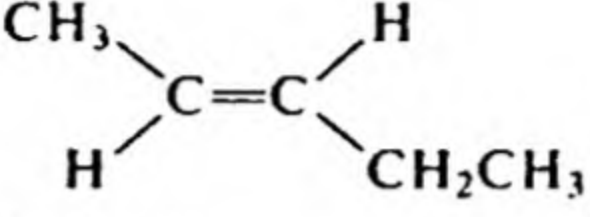
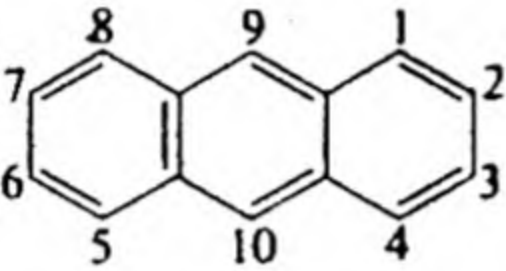
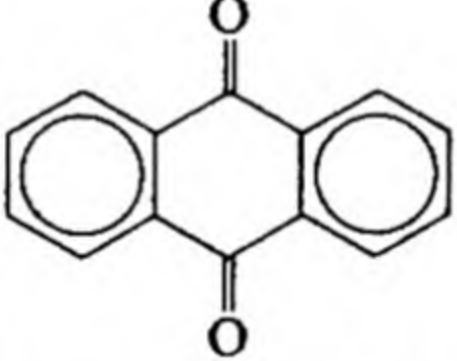
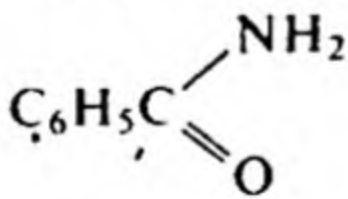





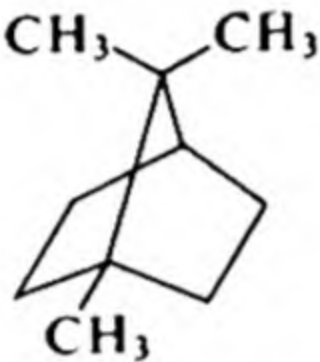
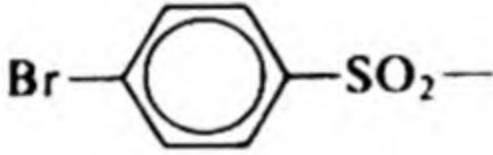
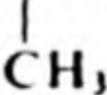
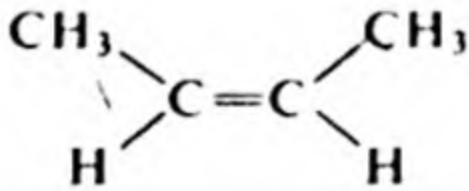
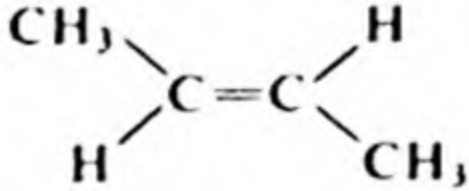
General Nomenclature Table

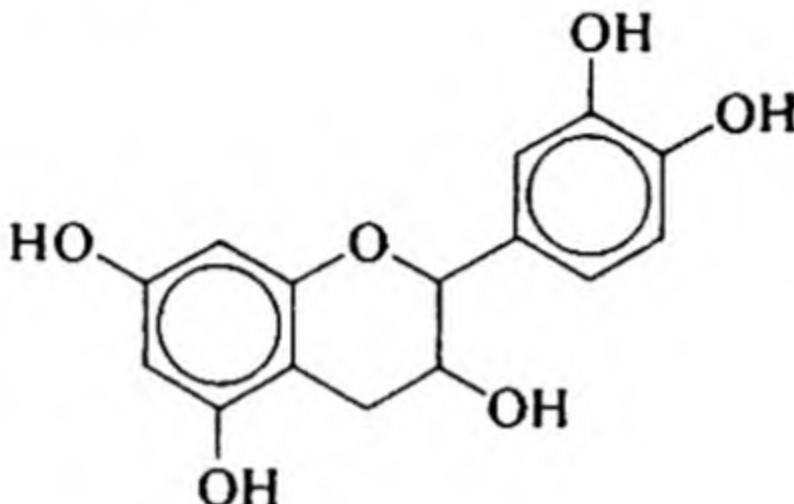
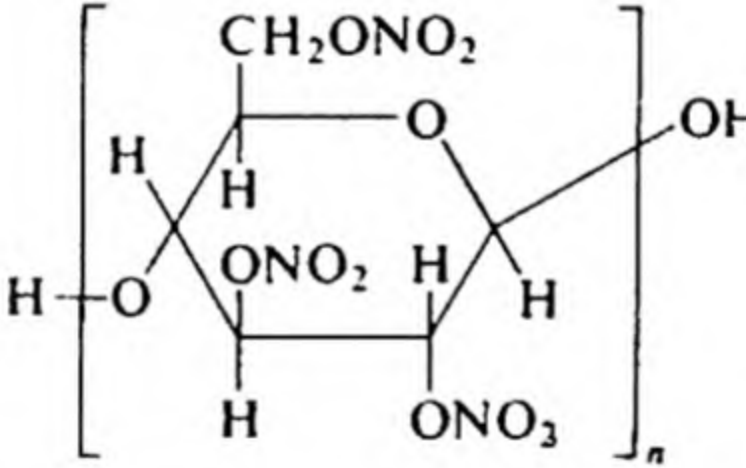
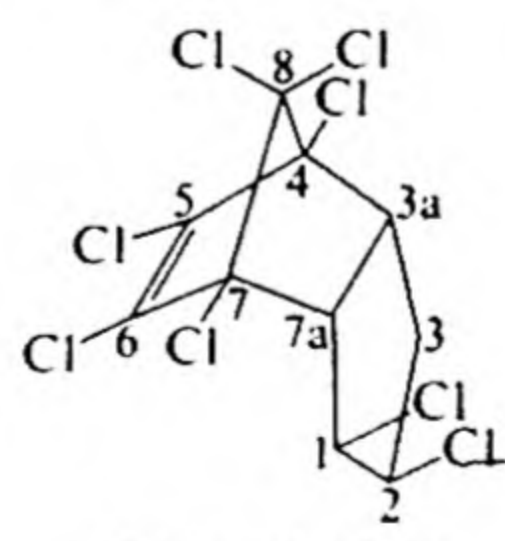
In the following table, compounds are listed alphabetically by their common names. Cross references are provided when more than one name is commonly used. Trivial (nonsystematic) names are given in boldface. Common names sanctioned by the IUPAC are marked with an asterisk. Names that differ from these, but are used in *Chemical Abstracts* indices, are identified by a superscript CA.

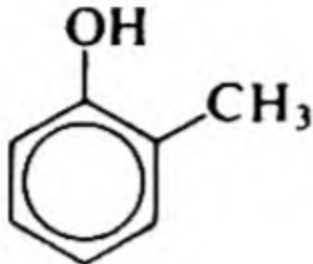
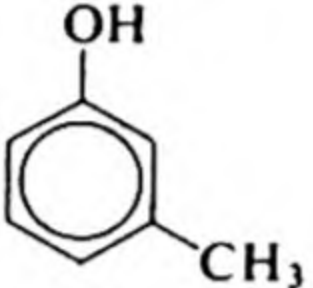
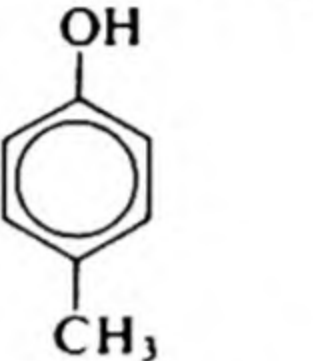

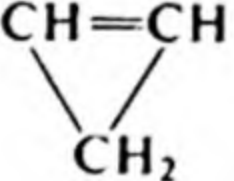

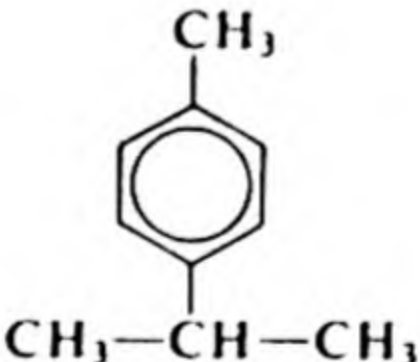
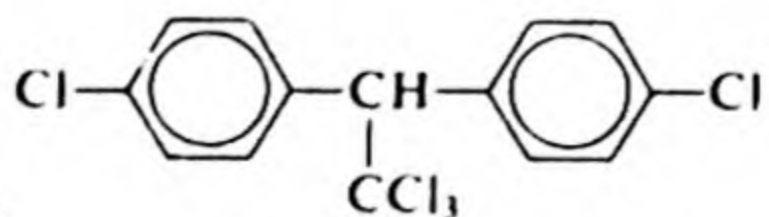
Common Name	Structure	IUPAC Rules Name
acetal		
diethyl acetal	$\begin{array}{c} \text{OC}_2\text{H}_5 \\ \diagup \\ \text{CH}_3\text{CH} \\ \diagdown \\ \text{OC}_2\text{H}_5 \end{array}$	1,1-diethoxyethane
acetaldehyde	CH_3CHO	ethanal
acetamide	CH_3CONH_2	ethanamide
acetamidine	$\begin{array}{c} \text{NH}_2 \\ \diagup \\ \text{CH}_3\text{C} \\ \diagdown \\ \text{NH} \end{array}$	ethanamidine
acetanilide		
antifebrin	$\text{C}_6\text{H}_5\text{NHCOCH}_3$	<i>N</i> -phenylethanamide
acetate*	CH_3CO_2-	ethanoate
prefix: acetoxy		prefix: ethanoyloxy
acetic acid*	$\text{CH}_3\text{CO}_2\text{H}$	ethanoic acid
aceto: see acetyl		
acetohydrazide	$\text{CH}_3\text{CONHNH}_2$	ethanohydrazide
acetohydroxamic acid	CH_3CONHOH	ethanohydroxamide
acetol	$\begin{array}{c} \text{CH}_3\text{CCH}_2\text{OH} \\ \parallel \\ \text{O} \end{array}$	1-hydroxy-2-propanone
acetone	CH_3COCH_3	propanone
acetonitrile	$\text{CH}_3\text{C}\equiv\text{N}$	ethanonitrile
acetophenone	$\text{C}_6\text{H}_5\text{COCH}_3$	1-phenylethanone


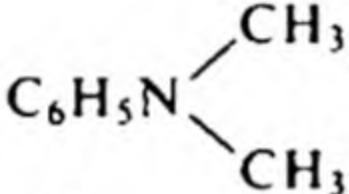
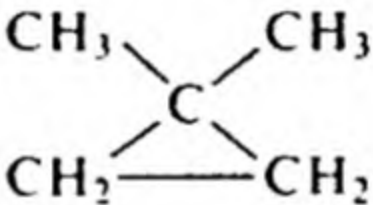
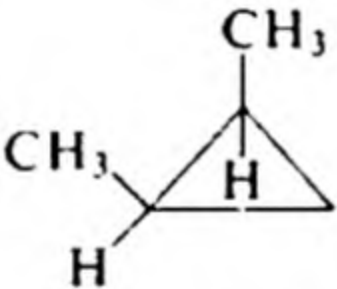
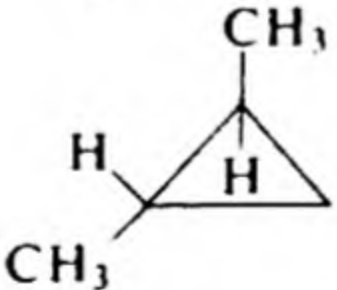
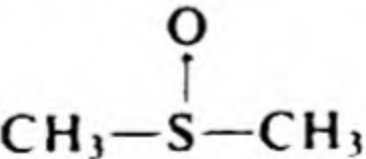
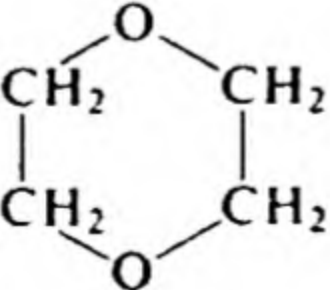
Common Name	Structure	IUPAC Rules Name
<i>p</i> -acetotoluidide <i>N</i> - <i>p</i> -tolylacetamide*		<i>N</i> -4-methylphenylethan- amide
acetoxy: see acetate acetyl*	$\text{CH}_3\text{C}(=\text{O})-$	ethanoyl
acetylene*	$\text{HC}\equiv\text{CH}$	ethyne
acetylenyl	$\text{HC}\equiv\text{C}-$	ethynyl
acetyl nitrate	$\text{CH}_3\text{C}(=\text{O})\text{ONO}_2$	ethanoyl nitrate
acrolein	$\text{CH}_2=\text{CHCH}=\text{O}$	2-propenal
acrylic acid	$\text{CH}_2=\text{CHCO}_2\text{H}$	propenoic acid
acrylonitrile	$\text{CH}_2=\text{CHC}\equiv\text{N}$	propenenitrile
adipic acid	$\text{HOCOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	hexanedioic acid
alanine	$\text{CH}_3\text{CH}(\text{NH}_3^+)\text{CO}_2^-$	2-aminopropanoic acid
aldrin 1,2,3,4,10,10-hexa- chloro-1,4,4a,5,8,8a- hexahydro-1,4:5,8- dimethanonaph- thalene	 (CA numbering)	1,8,9,10,11,11-hexachlo- rotetracyclo- [6.2.1.1 ^{3,6} .0 ^{2,7}]4,9- dodecadiene
allene	$\text{H}_2\text{C}=\text{C}=\text{CH}_2$	propadiene
allylamine*	$\text{CH}_2=\text{CHCH}_2\text{NH}_2$	2-propenylamine
allyl chloroformate chloroformic acid allyl ester ^{CA}	$\text{CH}_2=\text{CHCH}_2\text{OCOCI}$	2-propenoxymethanoyl chloride
allyl isothiocyanate* allyl mustard oil isothiocyanic acid allyl ester ^{CA}	$\text{CH}_2=\text{CHCH}_2\text{N}=\text{C}=\text{S}$	2-propenyl isothiocy- anate
allyl mercaptan allyl mustard oil: see allyl isothiocyanate	$\text{CH}_2=\text{CHCH}_2\text{SH}$	2-propene-1-thiol
<i>p</i> -aminobenzoic acid		4-aminobenzenecarbox- ylic acid
α - <i>n</i> -amylene	$\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{CH}_3$	1-pentene

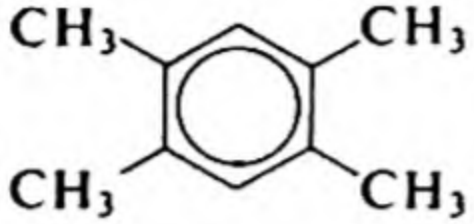
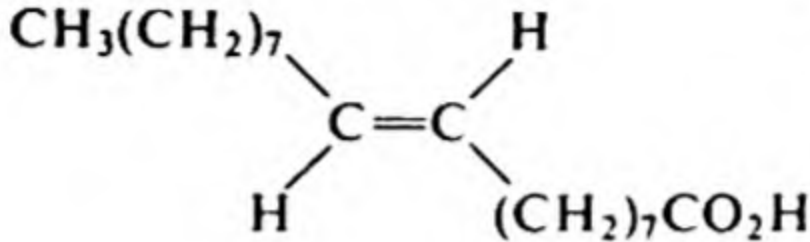
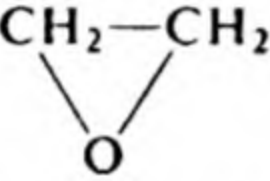
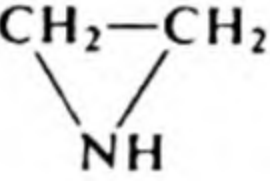
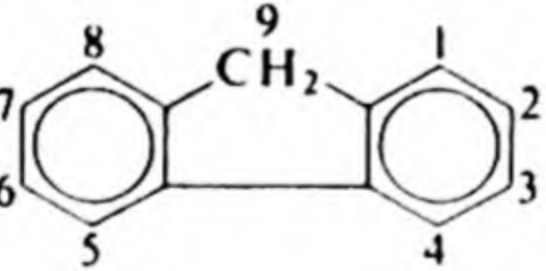
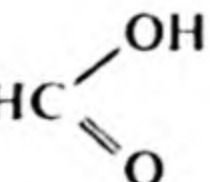
Common Name	Structure	IUPAC Rules Name
β -n-amylene		
<i>cis</i> :		<i>cis</i> -2-pentene
<i>trans</i> :		<i>trans</i> -2-pentene
aniline* anilinium chloride aniline hydrochloride ^{CA} anisole	$\text{C}_6\text{H}_5\text{NH}_2$ $\text{C}_6\text{H}_5\text{NH}_3^+ \text{Cl}^-$ $\text{C}_6\text{H}_5\text{OCH}_3$	phenylamine phenylammonium chloride methoxybenzene
anthracene*		anthracene
anthraquinone (9,10—*)		9,10-dihydroanthracene-9,10-dione
arachidic acid azelaic acid BAL British antilewisite α,β -dithioglycerol benzalaniline <i>N</i> -benzylideneaniline ^{CA} benzaldehyde	$\text{CH}_3(\text{CH}_2)_{18}\text{CO}_2\text{H}$ $\text{HOCO}(\text{CH}_2)_7\text{CO}_2\text{H}$ $\text{HSCH}_2\text{CH}(\text{SH})\text{CH}_2\text{OH}$ $\text{C}_6\text{H}_5\text{CH}=\text{NC}_6\text{H}_5$ $\text{C}_6\text{H}_5\text{CH}=\text{O}$	eicosanoic acid nonanedioic acid 2,3-dimercapto-1-propanol <i>N</i> ,1-diphenylmethyldeneimine benzenecarbaldehyde
benzamide		benzenecarbonamide
benzene*	 or C_6H_6	benzene
benzenesulfonamide benzenesulfonic acid benzoate prefix: benzoyloxy	$\text{C}_6\text{H}_5\text{SO}_2\text{NH}_2$ $\text{C}_6\text{H}_5\text{SO}_3\text{H}$ $\text{C}_6\text{H}_5\text{CO}_2-$	benzenesulfonamide benzenesulfonic acid benzenecarboxylate prefix: benzenecarboxy

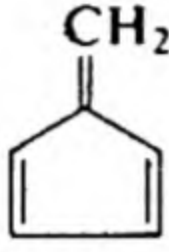

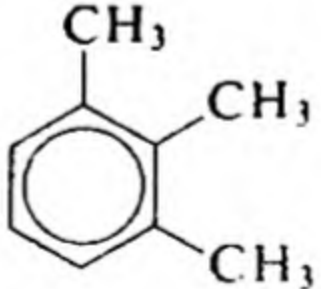
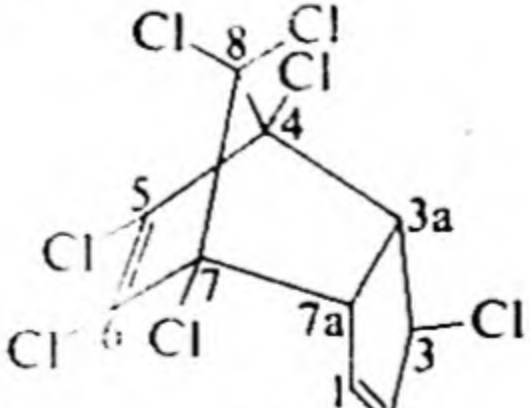
Common Name	Structure	IUPAC Rules Name
benzoic acid	$C_6H_5CO_2H$	benzenecarboxylic acid
benzonitrile	$C_6H_5C\equiv N$	benzenecarbonitrile
benzophenone	$C_6H_5COC_6H_5$	diphenylmethanone
benzoquinone (1,4—*) quinone ^{CA}		1,4-dihydro-1,4-benzene- dione 2,5-cyclohexadiene- 1,4-dione
benzoyl	C_6H_5C- 	oenzenecarbonyl
benzoyloxy: see benzoate		
benzyl alcohol	$C_6H_5CH_2OH$	phenylmethanol
bornane* camphane ^{CA}		1,7,7-trimethylbicyclo- [2.2.1]heptane
brassic acid British antilewisite: see BAL	$HOCO(CH_2)_{11}CO_2H$	tridecanedioic acid
<i>p</i> -bromobenzenesulfonyl brosyl		4-bromobenzenesulfonyl
bromoform	$CHBr_3$	tribromomethane
brosyl: see <i>p</i> -bromoben- zenesulfonyl		
butadiene	$CH_2=CHCH=CH_2$	1,3-butadiene
2°-butylamine*	$CH_3CH_2CHNH_2$ 	1-methylpropylamine
α -butylene	$CH_2=CHCH_2CH_3$	1-butene
β -butylene		
<i>cis</i>		<i>cis</i> -2-butene
<i>trans</i>		<i>trans</i> -2-butene
<i>n</i> -butyraldehyde	$CH_3CH_2CH_2CHO$	butanal
<i>n</i> -butyric acid	$CH_3CH_2CH_2CO_2H$	butanoic acid
cadaverine	$H_2N(CH_2)_5NH_2$	pentamethylenediamine


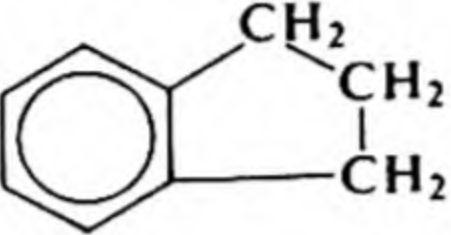

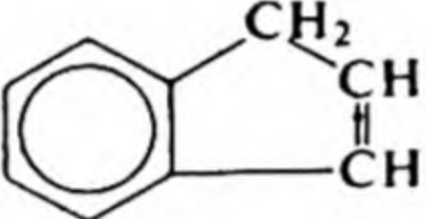
Common Name	Structure	IUPAC Rules Name
camphane: see bornane		
<i>n</i> -capraldehyde	$\text{CH}_3(\text{CH}_2)_8\text{CHO}$	decanal
<i>n</i> -capric acid	$\text{CH}_3(\text{CH}_2)_8\text{CO}_2\text{H}$	decanoic acid
<i>n</i> -caproaldehyde	$\text{CH}_3(\text{CH}_2)_4\text{CHO}$	hexanal
<i>n</i> -caproic acid	$\text{CH}_3(\text{CH}_2)_4\text{CO}_2\text{H}$	hexanoic acid
<i>n</i> -caprylaldehyde	$\text{CH}_3(\text{CH}_2)_6\text{CHO}$	octanal
<i>n</i> -caprylic acid	$\text{CH}_3(\text{CH}_2)_6\text{CO}_2\text{H}$	octanoic acid
carbamide: see urea		
carbonic acid*	$\begin{array}{c} \text{HO} \text{---} \text{C} \text{---} \text{OH} \\ \\ \text{O} \end{array}$	hydroxymethanoic acid
catechol (see also pyrocatechol)		2-(3,4-dihydroxyphenyl)- 1,2,3,4-tetrahydro-1- oxanaphthalene-3,5,7- triol
cellulose trinitrate* nitrocellulose ^{CA} cordite (about 2.7 ni- trate groups per unit)		
ceryl alcohol	$\text{CH}_3(\text{CH}_2)_{25}\text{OH}$	1-hexacosanol
cetyl alcohol	$\text{CH}_3(\text{CH}_2)_{15}\text{OH}$	1-hexadecanol
chlordan 1,2,4,5,6,7,8,8-octa- chloro-3a,4,7,7a- tetrahydro-4,7- methanoindan ^{CA}	 <p>(CA numbering)</p>	1,3,4,7,8,9,10,10-octa- chloro-8-tricyclo- [5.2.1.0 ^{2,6}]decene
chloroform	CHCl_3	trichloromethane
cinnamaldehyde	$\text{C}_6\text{H}_5\text{CH}=\text{CHCHO}$	3-phenyl-2-propenal
cordite: see cellulose nitrate		

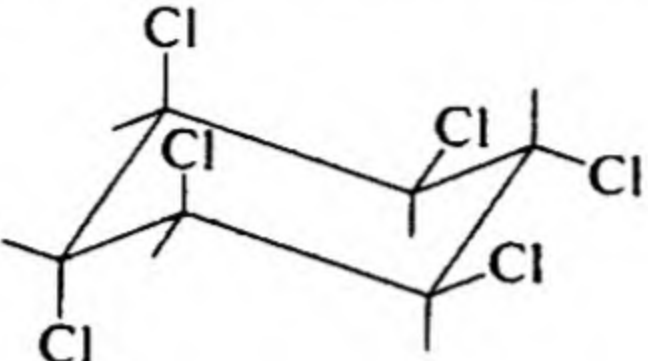
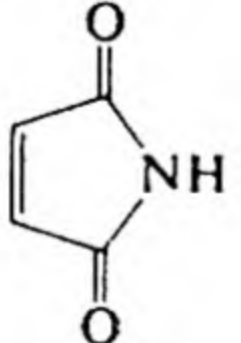
Common Name	Structure	IUPAC Rules Name
cresol		
<i>o</i> -		2-methylphenol
<i>m</i> -		3-methylphenol
<i>p</i> -		4-methylphenol
crotonaldehyde crotonic acid cumene*	$\text{CH}_3\text{CH}=\text{CHCHO}$ $\text{CH}_3\text{CH}=\text{CHCO}_2\text{H}$ $\text{CH}_3\text{CH}(\text{C}_6\text{H}_5)\text{CH}_3$	2-butenal 2-butenic acid 1-methylethylbenzene 2-phenylpropane
cyanamide cyanogen	$\text{H}_2\text{NC}\equiv\text{N}$ $\text{N}\equiv\text{C}-\text{C}\equiv\text{N}$	aminomethanonitrile ethanedinitrile
cyclohexanone		cyclohexanone
cyclopropene	 or 	cyclopropene
<i>p</i> -cymene*		1-methyl-4-(1-methylethyl)benzene
DDT dichlorodiphenyltri- chloroethane; 1,1,1- trichloro-2,2-bis(<i>p</i> - chlorophenyl)ethane ^{CA}		1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane

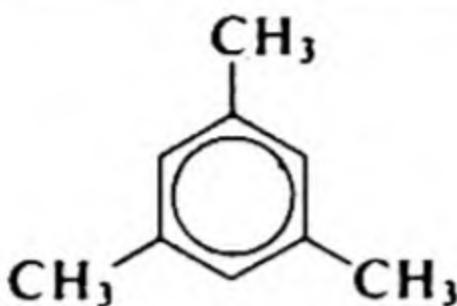
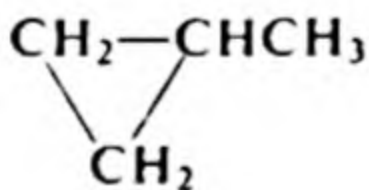
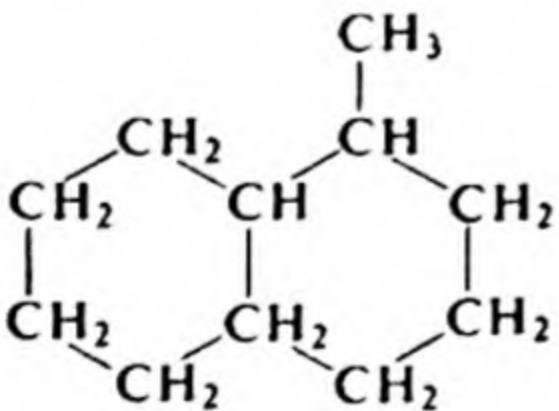
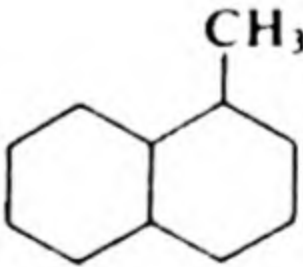
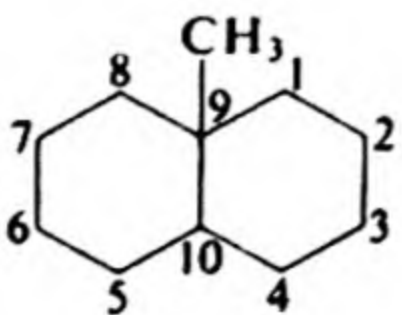
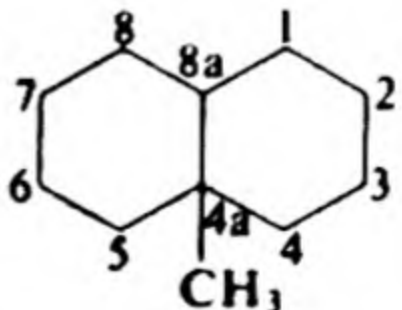
Common Name	Structure	IUPAC Rules Name
<i>p</i> -dichlorobenzene		1,4-dichlorobenzene
diethanolamine 2,2-iminodiethanol ^{CA}	$(\text{HOCH}_2\text{CH}_2)_2\text{NH}$	bis(2-hydroxyethyl)- amine
diethylenetriamine	$(\text{H}_2\text{NCH}_2\text{CH}_2)_2\text{NH}$	bis(2-aminoethyl)amine
diisopropyl	$\text{CH}_2\text{CH}(\text{CH}_3)-\text{CH}(\text{CH}_3)\text{CH}_3$	2,3-dimethylbutane
dimethylacetylene	$\text{CH}_3\text{C}\equiv\text{CCH}_3$	2-butyne
dimethylamine sulfate	$[(\text{CH}_3)_2\text{NH}_2^+]_2\text{SO}_4^{2-}$	dimethylammonium sulfate
<i>N,N</i> -dimethylaniline		<i>N,N</i> -dimethylphenyl- amine
<i>gem</i> -dimethylcyclopropane		1,1-dimethylcyclopropane
<i>vic</i> -dimethylcyclopropane		
<i>cis</i>		<i>cis</i> -1,2-dimethylcyclopropane
<i>trans</i>		<i>trans</i> -1,2-dimethylcyclopropane
dimethyl sulfoxide DMSO methyl sulfoxide ^{CA}		methylsulfinylmethane
dioxane <i>p</i> -dioxane ^{CA}		1,4-dioxane 1,4-dioxinane
ditane α,β -dithioglycerol: see BAL	$\text{C}_6\text{H}_5\text{CH}_2\text{C}_6\text{H}_5$	diphenylmethane

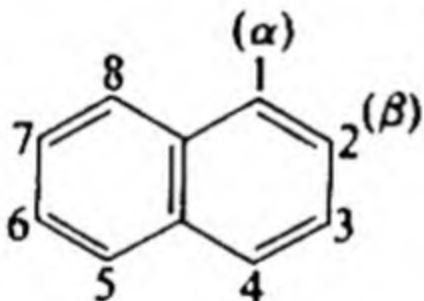
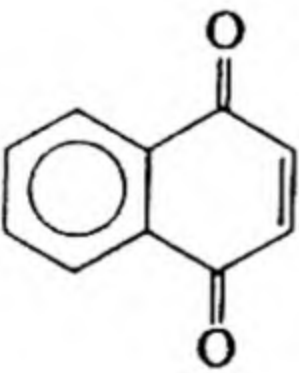
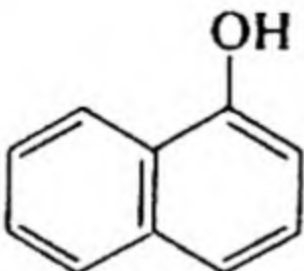
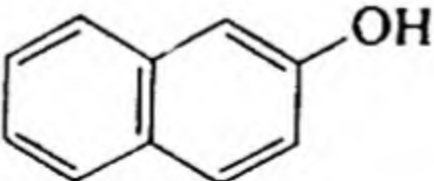
Common Name	Structure	IUPAC Rules Name
durene		1,2,4,5-tetramethylbenzene
elaidic acid		<i>trans</i> -9-octadecenoic acid
<i>n</i> -enanthaldehyde: see heptaldehyde		
<i>n</i> - enanthic acid	$\text{CH}_3(\text{CH}_2)_5\text{CO}_2\text{H}$	heptanoic acid
ethanolamine	$\text{HOCH}_2\text{CH}_2\text{NH}_2$	2-hydroxyethylamine
2-aminoethanol ^{CA}		
ether : see ethyl ether		
ethylene*	$\text{H}_2\text{C}=\text{CH}_2$	ethene
ethylenediamine	$\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2$	ethylenediamine
ethylene glycol	$\text{HOCH}_2\text{CH}_2\text{OH}$	1,2-ethanediol
glycol		
ethylene oxide		epoxyethane oxirane
ethylenimine		aziridine
ethyl ether	$(\text{CH}_3\text{CH}_2)_2\text{O}$	ethoxyethane
ether		
ethyl phenyl ketone : see propiophenone		
<i>sym</i> -ethyl phenyl urea	$\text{CH}_3\text{CH}_2\text{NHCONHC}_6\text{H}_5$	<i>N</i> -ethyl- <i>N'</i> -phenylurea
fluorene*		fluorene
formaldehyde	$\text{H}-\text{C}-\text{H}$ \parallel O	methanal
formate	HCO_2-	methanoate
prefix: formoxy		prefix: methanoyloxy
formic acid*		methanoic acid

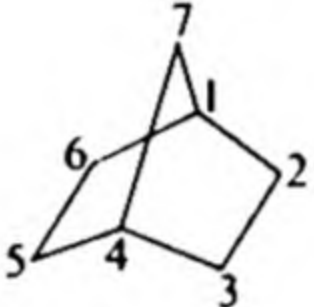
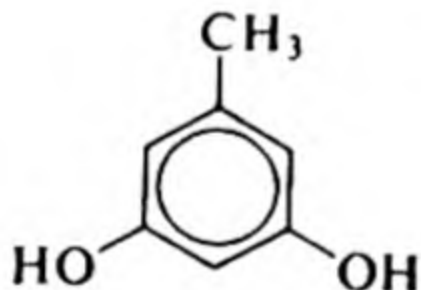
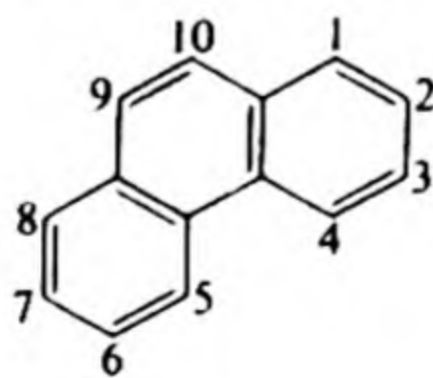
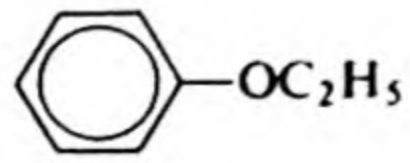
Common Name	Structure	IUPAC Rules Name
formoxy: see formate formyl*	$\text{HC}-\text{O}$ \parallel O	methanoyl: formyl preferred
fulvene	$ \begin{array}{c} \text{CH}_2 \\ \parallel \\ \text{C} \\ \diagup \quad \diagdown \\ \text{CH} \quad \text{CH} \\ \parallel \quad \parallel \\ \text{CH} - \text{CH} \end{array} $ or 	5-methyldiene-1,3-cyclopentadiene
fumaric acid	$ \begin{array}{c} \text{HOCOCH} \\ \parallel \\ \text{HC}-\text{CO}_2\text{H} \end{array} $	<i>trans</i> -butenedioic acid
furan		oxole
glutaric acid	$\text{HOCO}(\text{CH}_2)_3\text{CO}_2\text{H}$	pentanedioic acid
glycerol	$ \begin{array}{c} \text{HOCH}_2\text{CHCH}_2\text{OH} \\ \\ \text{OH} \end{array} $	1,2,3-propanetriol
glyceryl trinitrate nitroglycerin ^{CA}	$ \begin{array}{c} \text{O}_2\text{NOCH}_2\text{CHCH}_2\text{ONO}_2 \\ \\ \text{ONO}_2 \end{array} $	1,2,3-propane trinitrate
glycine aminoacetic acid	$ \begin{array}{c} \text{H}_3\text{N}^+\text{CH}_2\text{CO}_2^- \end{array} $	aminoethanoic acid
glycol: see ethylene glycol		
glycolic acid hydroxyacetic acid*	$\text{HOCH}_2\text{CO}_2\text{H}$	hydroxyethanoic acid
glyoxalic acid glyoxylic acid ^{CA}	$ \begin{array}{c} \text{HCCO}_2\text{H} \\ \parallel \\ \text{O} \end{array} $	oxoethanoic acid
guanidine*	$ \begin{array}{c} \text{H}_2\text{NCNH}_2 \\ \parallel \\ \text{NH} \end{array} $	guanidine
hemimellitene		1,2,3-trimethylbenzene
heptachlor 3,4,5,6,7,8,8-hepta- chloro-3a,4,7,7a- tetrahydro-4,7- methanoindene ^{CA}	 (CA Numbering)	1,5,7,8,9,10,10-hepta- chloro-3,8-tricyclo- [5.2.1.0 ^{2,6}]decadiene

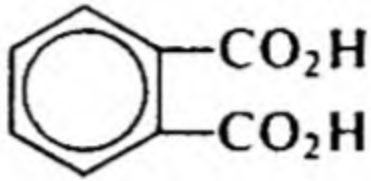
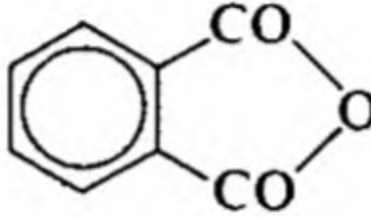
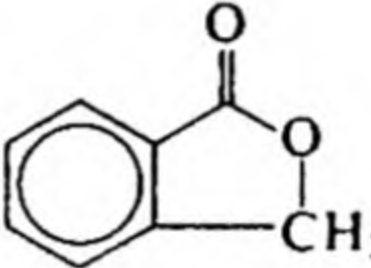
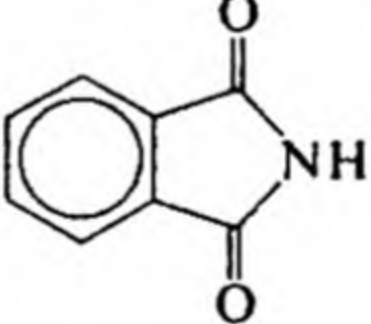
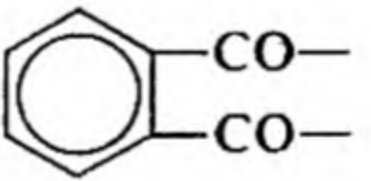
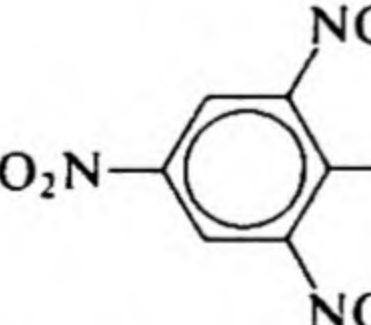
Common Name	Structure	IUPAC Rules Name
<i>n</i> -heptaldehyde <i>n</i> -enanthaldehyde	$\text{CH}_3(\text{CH}_2)_5\text{CHO}$	heptanal
hexahydrobenzoic acid		cyclohexanecarboxylic acid
1,6-hexanediamine	$\text{H}_2\text{N}(\text{CH}_2)_6\text{NH}_2$	hexamethylenediamine
hydrindene indan ^{CA}		1,2-dihydroindene
hydrogen cyanide hydrocyanic acid ^{CA}	$\text{HC}\equiv\text{N}$	methanonitrile
hydroquinone <i>p</i> -dihydroxybenzene		1,4-benzenediol
indene*		indene
iodoform	CHI_3	triiodomethane
isoamyl nitrite amyl nitrite ^{CA}	$(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{ON}=\text{O}$	3-methylbutyl nitrite
isobutylene	$(\text{CH}_3)_2\text{C}=\text{CH}_2$	2-methylpropene
isobutyraldehyde	$(\text{CH}_3)_2\text{CHCHO}$	2-methylpropanal
isooctane (improper name)	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{CCH}_2\text{CHCH}_3 \\ \quad \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$	2,2,4-trimethylpentane
isoprene	$\begin{array}{c} \text{CH}_2=\text{CCH}=\text{CH}_2 \\ \\ \text{CH}_3 \end{array}$	2-methyl-1,3-butadiene
isopropylethylene	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{CHCH}=\text{CH}_2 \end{array}$	3-methyl-1-butene
isovaleraldehyde	$(\text{CH}_3)_2\text{CHCH}_2\text{CHO}$	3-methylbutanal
ketene*	$\text{CH}_2=\text{C}=\text{O}$	ketene
lactic acid	$\begin{array}{c} \text{CH}_3\text{CHCO}_2\text{H} \\ \\ \text{OH} \end{array}$	2-hydroxypropanoic acid
lauric acid	$\text{CH}_3(\text{CH}_2)_{10}\text{CO}_2\text{H}$	dodecanoic acid
<i>n</i> -lauryl alcohol dodecyl alcohol ^{CA}	$\text{CH}_3(\text{CH}_2)_{10}\text{CH}_2\text{OH}$	1-dodecanol

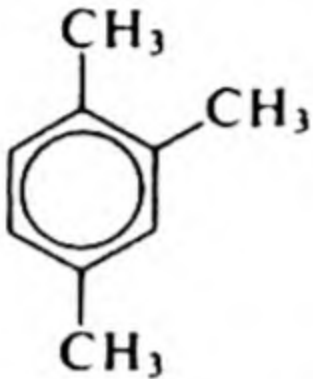

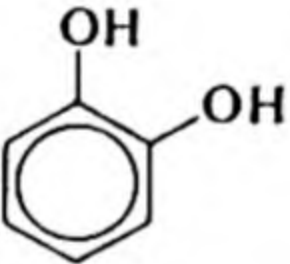
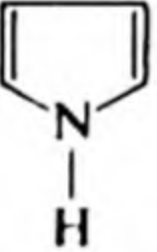
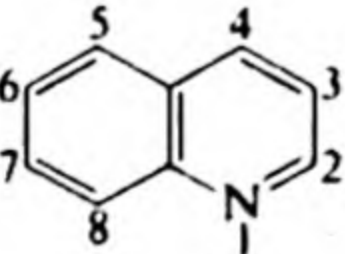
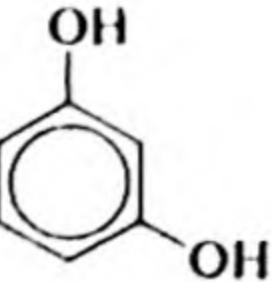
Common Name	Structure	IUPAC Rules Name
lindane γ -benzene hexachloride		1,2,3,4,5,6-hexachloro-cyclohexane (one stereoisomer)
linoleic acid	$\text{CH}_3(\text{CH}_2)_4 \begin{array}{c} \diagup \\ \text{C}=\text{C} \\ \diagdown \end{array} \begin{array}{c} \text{CH}_2 \\ \diagup \end{array} \begin{array}{c} \diagdown \\ \text{C}=\text{C} \\ \diagup \end{array} (\text{CH}_2)_7\text{CO}_2\text{H}$ <p style="text-align: center;">H H H</p>	<i>cis,cis</i> -9,12-octadecadienoic acid
linolenic acid	$\text{CH}_3\text{CH}_2 \begin{array}{c} \diagup \\ \text{C}=\text{C} \\ \diagdown \end{array} \begin{array}{c} \text{CH}_2 \\ \diagup \end{array} \begin{array}{c} \diagdown \\ \text{C}=\text{C} \\ \diagup \end{array} \begin{array}{c} \text{CH}_2 \\ \diagup \end{array} \begin{array}{c} \diagdown \\ \text{C}=\text{C} \\ \diagup \end{array} (\text{CH}_2)_7\text{CO}_2\text{H}$ <p style="text-align: center;">H H H H</p>	<i>cis,cis,cis</i> -9,12,15-octadecatrienoic acid
maleic acid	$\begin{array}{c} \text{O} \\ \parallel \\ \text{HC}-\text{COH} \\ \parallel \\ \text{HC}-\text{COH} \\ \parallel \\ \text{O} \end{array}$	<i>cis</i> -butenedioic acid
maleic anhydride	$\begin{array}{c} \text{O} \\ \parallel \\ \text{HC}-\text{C} \\ \parallel \quad \diagup \\ \text{HC}-\text{C} \quad \text{O} \\ \parallel \\ \text{O} \end{array} \quad \text{or} \quad \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{O} \\ \parallel \\ \text{O} \end{array}$	<i>cis</i> -butenedioic anhydride
maleimide		<i>cis</i> -butenedioimide
malic acid	$\text{HOCOCH} \begin{array}{c} \\ \text{OH} \end{array} \text{CH}_2\text{CO}_2\text{H}$	2-hydroxybutanedioic acid
malonic acid malononitrile	$\text{HOCOCH}_2\text{CO}_2\text{H}$ $\text{N}\equiv\text{CCH}_2\text{C}\equiv\text{N}$	propanedioic acid propanedinitrile

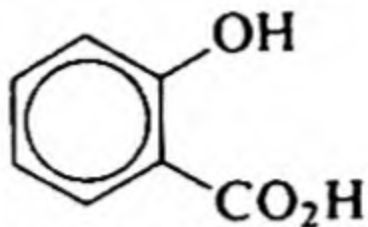
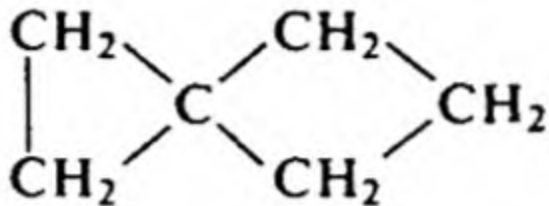
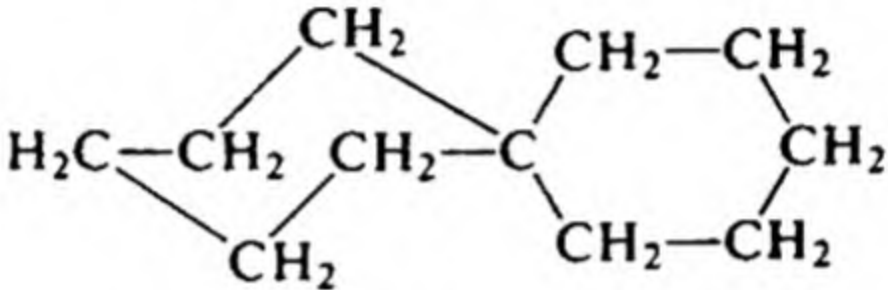
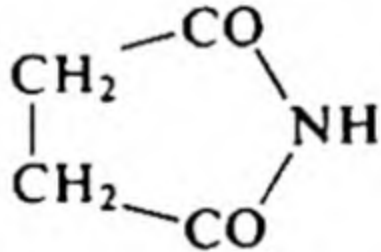

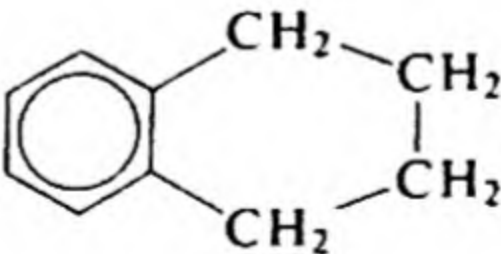
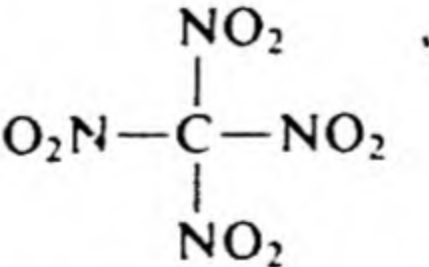
Common Name	Structure	IUPAC Rules Name
mesitylene*		1,3,5-trimethylbenzene
methacrolein methacrylaldehyde ^{CA}	$\begin{array}{c} \text{CH}_2=\text{CCHO} \\ \\ \text{CH}_3 \end{array}$	2-methyl-2-propenal
methacrylic acid	$\begin{array}{c} \text{CH}_2=\text{CCO}_2\text{H} \\ \\ \text{CH}_3 \end{array}$	2-methylpropenoic acid
methylacetylene	$\text{CH}_3\text{C}\equiv\text{CH}$	propyne
methyl acid sulfate	$\text{CH}_3\text{OSO}_2\text{OH}$	methyl hydrogen sulfate
methylsulfuric acid ^{CA}		
methylamine hydrochloride	$\text{CH}_3\text{NH}_3^+\text{Cl}^-$	methylammonium chloride
<i>N</i> -methylaniline	$\text{C}_6\text{H}_5\text{NHCH}_3$	<i>N</i> -methylphenylamine
methyl-2°-butylamine*	$\begin{array}{c} \text{CH}_3\text{CH}_2\text{CH}-\text{NH}-\text{CH}_3 \\ \\ \text{CH}_3 \end{array}$	methyl(1-methylpropyl)-amine
methyl carbylamine: see methyl isocyanide		
methyl cyanide: see acetonitrile		
methylcyclopropane		methylcyclopropane
α-methyldecalin (4 stereoisomers)	 or 	decahydro-1-methylnaphthalene
9-methyldecalin (2 stereoisomers)	 or 	decahydro-4a-methylnaphthalene

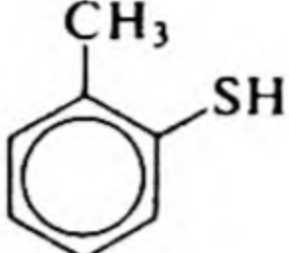
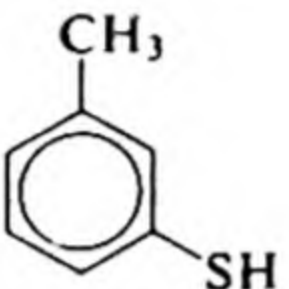
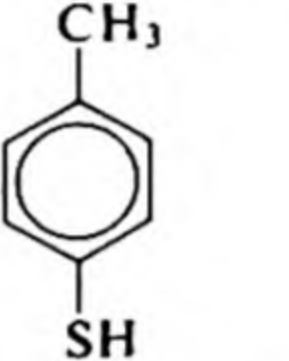

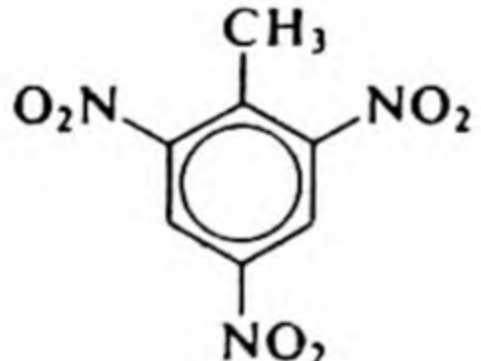

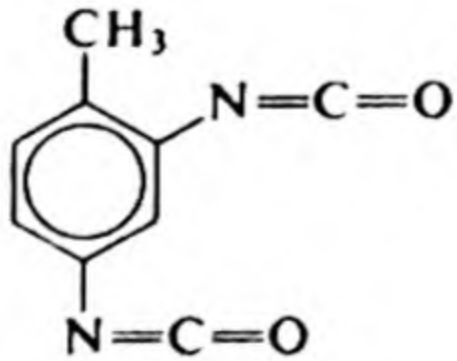

Common Name	Structure	IUPAC Rules Name
methyl disulfide	CH_3SSCH_3	methyldithiomethane
methyl ether	CH_3OCH_3	methoxymethane
dimethyl ether		
methyl ethyl ketone	$\text{CH}_3\text{CH}_2\text{C}(=\text{O})\text{CH}_3$	butanone
	O	
	O	
methyl ethyl sulfone	$\text{CH}_3\text{CH}_2\text{S}(=\text{O})_2\text{CH}_3$	methylsulfonyl ethane
	O	
methyl isocyanide	$\text{CH}_3\text{N}=\text{C}=\text{O}$	methyl isocyanide
methyl nitrate	CH_3ONO_2	methyl nitrate
methyl sulfate	$\text{CH}_3\text{OSO}_2\text{OCH}_3$	methyl sulfate
monothioglycol	$\text{HSCH}_2\text{CH}_2\text{OH}$	2-mercaptoethanol
mustard gas	$(\text{ClCH}_2\text{CH}_2)_2\text{S}$	1-chloro-2-(2-chloroethylthio)ethane
bis(2-chloroethyl)sulfide ^{CA}		
mustard oil:		
see allyl isothiocyanate		
myricyl alcohol	$\text{CH}_3(\text{CH}_2)_{29}\text{CH}_2\text{OH}$	1-untriacontanol
myristic acid	$\text{CH}_3(\text{CH}_2)_{12}\text{CO}_2\text{H}$	tetradecanoic acid
myristyl alcohol	$\text{CH}_3(\text{CH}_2)_{12}\text{CH}_2\text{OH}$	1-tetradecanol
naphthalene*		naphthalene
naphthaquinone		1,4-naphthaquinone
1,4-naphthoquinone ^{CA}		
α-naphthol		1-naphthol
β-naphthol		2-naphthol
nitrobenzene	$\text{C}_6\text{H}_5\text{NO}_2$	nitrobenzene

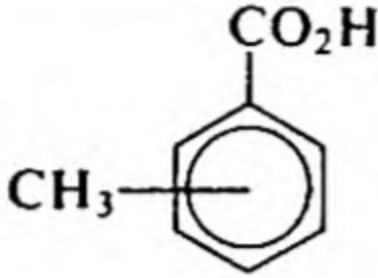
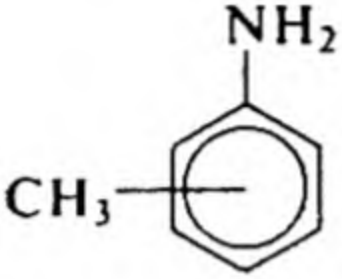
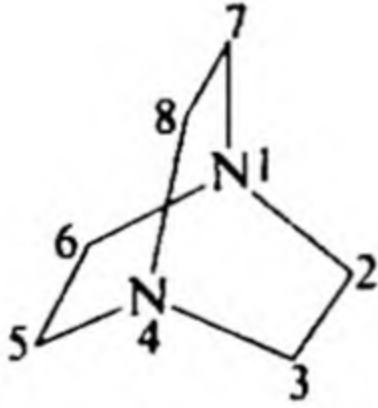
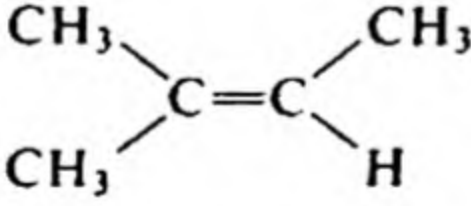
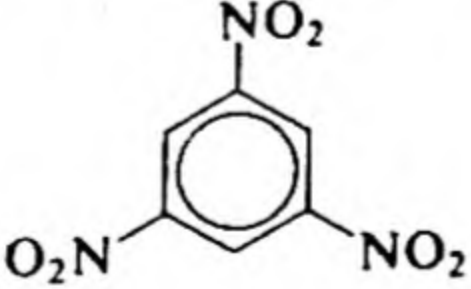
Common Name	Structure	IUPAC Rules Name
nitrocellulose (improper name): see cellulose nitrate		
nitroform	$\begin{array}{c} \text{NO}_2 \\ \\ \text{HC}-\text{NO}_2 \\ \\ \text{NO}_2 \end{array}$	trinitromethane
nitroglycerin (improper name): see glyceryl trinitrate		
nitromethane	$\begin{array}{c} \text{CH}_3\text{NO}_2 \\ \text{CH}_2=\text{NOH} \\ \\ \text{O} \end{array}$	nitromethane
aci-nitromethane		aci-nitromethane
norbornane* norcamphane ^{CA}		bicyclo[2.2.1]heptane
oleic acid	$\begin{array}{c} \text{CH}_3(\text{CH}_2)_7 \quad \quad \quad (\text{CH}_2)_7\text{CO}_2\text{H} \\ \quad \quad \quad \diagdown \quad \diagup \\ \quad \quad \quad \text{C}=\text{C} \\ \quad \quad \quad \diagup \quad \diagdown \\ \text{H} \quad \quad \quad \text{H} \end{array}$	cis-octadecenoic acid
orcinol toluene-3,5-diol*		5-methylbenzene-1,3-diol
oxalamide oxamide ^{CA}	$\text{H}_2\text{NCOCONH}_2$	ethanediamide
oxalic acid*	HOCOCO_2H	ethanedioic acid
palmitic acid	$\text{CH}_3(\text{CH}_2)_{14}\text{CO}_2\text{H}$	hexadecanoic acid
n-pelargonaldehyde	$\text{CH}_3(\text{CH}_2)_7\text{CHO}$	nonanal
n-pelargonic acid	$\text{CH}_3(\text{CH}_2)_7\text{CO}_2\text{H}$	nonanoic acid
phenanthrene*		phenanthrene
phenetole		ethoxybenzene

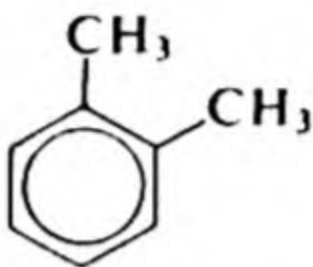
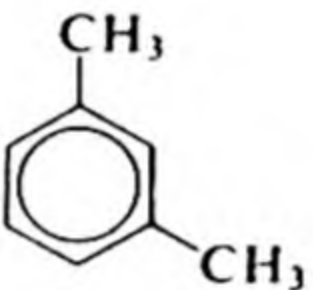
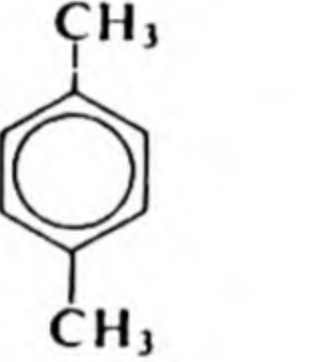
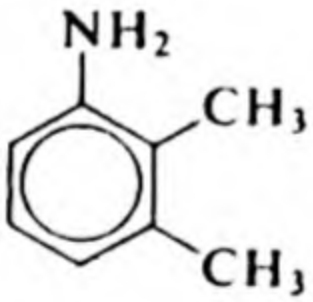
Common Name	Structure	IUPAC Rules Name
phenol	C_6H_5OH	phenol
phenylacetic acid	$C_6H_5CH_2CO_2H$	phenylethanoic acid
phenylhydrazine	$C_6H_5NHNH_2$	phenylhydrazine
phenylhydrazine hydrochloride	$C_6H_5NHNH_3^+Cl^-$	phenylhydrazinium chloride
phenyl isocyanate	$C_6H_5N=C=O$	phenyl isocyanate
phenyl sulfone	$C_6H_5SO_2C_6H_5$	phenylsulfonylbenzene
phthalic acid		1,2-benzenedicarboxylic acid
phthalic anhydride		1,2-benzenedicarboxylic anhydride
phthalide		2,3-dihydro-2-oxa-1-indenone
phthalimide		1,2-benzenedicarbonyl imide
phthaloyl		1,2-benzenedicarbonyl
phytol	$(CH_3)_2CH(CH_2)_3\underset{\text{CH}_3}{\underset{ }{CH}}(CH_2)_3\underset{\text{CH}_3}{\underset{ }{CH}}(CH_2)_3\underset{\text{CH}_3}{\underset{ }{C}}=CHCH_2OH$	3,7,11,15-tetramethyl-2-hexadecen-1-ol
picric acid		2,4,6-trinitrophenol
pimelic acid	$HOCO(CH_2)_5CO_2H$	heptanedioic acid
pivalaldehyde	$(CH_3)_3CCHO$	2,2-dimethylpropanal
trimethylacetaldehyde		
pivalic acid	$(CH_3)_3CCO_2H$	2,2-dimethylpropanoic acid
trimethylacetic acid		

Common Name	Structure	IUPAC Rules Name
potassium ethyl sulfate ethyl potassium sul- fate ^{CA}	$\text{CH}_3\text{CH}_2\text{OSO}_3^- \text{K}^+$	potassium ethyl sulfate
propionic acid propiophenone ethyl phenyl ketone	$\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$ $\text{C}_6\text{H}_5\text{C}(=\text{O})\text{CH}_2\text{CH}_3$	propanoic acid 1-phenyl-1-propanone
propylene	$\text{CH}_3\text{CH}=\text{CH}_2$	propene
pseudocumene		1,2,4-trimethylbenzene
putrescine	$\text{H}_2\text{N}(\text{CH}_2)_4\text{NH}_2$	tetramethylenediamine
pyridine		azine
pyrocatechol ^{CA} catechol (which see)		1,2-benzenediol
pyrrole		azole
pyruvic acid	$\text{CH}_3-\text{C}(=\text{O})-\text{CO}_2\text{H}$	2-oxopropanoic acid
quinoline		1-azanaphthalene
quinone: see benzoquinone		
resorcinol		1,3-benzenediol

Common Name	Structure	IUPAC Rules Name
salicylic acid <i>o</i> -hydroxybenzoic acid		2-hydroxybenzenecarboxylic acid
sebacic acid semicarbazide*	$\text{HOCO}(\text{CH}_2)_8\text{CO}_2\text{H}$ $\text{H}_2\text{NCONHNH}_2$	decanedioic acid semicarbazide
spirohexane		spirohexane
<i>sym</i>-spiroundecane		spiro[5.5]undecane
stearic acid styrene	$\text{CH}_3(\text{CH}_2)_{16}\text{CO}_2\text{H}$ $\text{C}_6\text{H}_5\text{CH}=\text{CH}_2$	octadecanoic acid phenylethene; vinylbenzene (rather than ethenylbenzene)
suberic acid succinic acid	$\text{HOCO}(\text{CH}_2)_6\text{CO}_2\text{H}$ $\text{HOCOCH}_2\text{CH}_2\text{CO}_2\text{H}$	octanedioic acid butanedioic acid
succinimide		butanediimide
tetraethylammonium iodide	$(\text{CH}_3\text{CH}_2)_4\text{N}^+\text{I}^-$	tetraethylammonium iodide
tetrahydrofuran THF		oxolane
tetralin		1,2,3,4-tetrahydronaphthalene
tetranitromethane		tetranitromethane
thapsic acid thioanisole methyl phenyl sulfide ^{CA}	$\text{HOCO}(\text{CH}_2)_{14}\text{CO}_2\text{H}$ $\text{C}_6\text{H}_5\text{SCH}_3$	hexadecanedioic acid methylthiobenzene

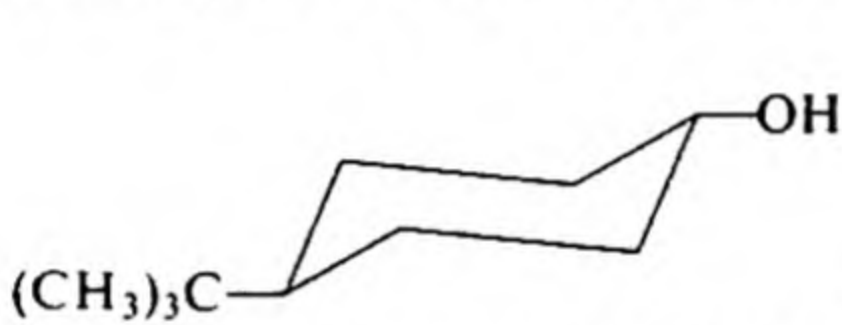
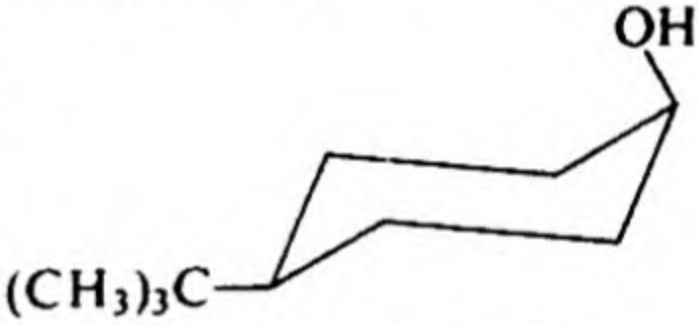
Common Name	Structure	IUPAC Rules Name
thiocresol toluenethiol ^{CA}		
<i>o</i> -		2-methylbenzenethiol
<i>m</i> -		3-methylbenzenethiol
<i>p</i> -		4-methylbenzenethiol
thiodiglycol 2,2'-thiodiethanol ^{CA}	HOCH ₂ CH ₂ SCH ₂ CH ₂ OH	2-(2-hydroxyethylthio)-ethanol
thiophene*		thiole
thiophenol	C ₆ H ₅ SH	benzenethiol
TNT trinitrotoluene (2,4,6—*)		2,4,6-trinitro-1-methylbenzene
<i>p</i> -tolualdehyde		4-methylbenzenecarbaldehyde
toluene*	C ₆ H ₅ CH ₃	methylbenzene phenylmethane
toluene diisocyanate 2,4-diisocyanatotoluene ^{CA} 4-methyl- <i>m</i> -phenylene diisocyanate		4-methylbenzene-1,3-diisocyanate
<i>p</i> -toluenesulfonyl ^{CA} tosyl		4-methylbenzenesulfonyl

Common Name	Structure	IUPAC Rules Name
toluic acid		methylbenzenecarboxylic acid
<i>o</i> -		2-
<i>m</i> -		3-
<i>p</i> -		4-
toluidine tolylamine*		methylphenylamine
<i>o</i> -		2-
<i>m</i> -		3-
<i>p</i> -		4-
tosyl: see <i>p</i> -toluenesulfonyl		
triethylenediamine		1,4-diazabicyclo[2.2.2]octane
trimethylacetaldehyde: see pivalaldehyde		
trimethylamine acid sulfate	$(\text{CH}_3)_3\text{NH}^+\text{HSO}_4^-$	trimethylammonium hydrogen sulfate
trimethylethylene		2-methyl-2-butene
trinitrobenzene TNB		1,3,5-trinitrobenzene
trinitrotoluene: see TNT		
triphenylcarbinol	$(\text{C}_6\text{H}_5)_3\text{COH}$	triphenylmethanol
tristearin glyceryl tristearate stearin ^{CA}	$\begin{array}{c} \text{CH}_2\text{OCO}(\text{CH}_2)_{16}\text{CH}_3 \\ \\ \text{CHOCO}(\text{CH}_2)_{16}\text{CH}_3 \\ \\ \text{CH}_2\text{OCO}(\text{CH}_2)_{16}\text{CH}_3 \end{array}$	1,2,3-propane trioctadecanoate

Common Name	Structure	IUPAC Rules Name
tritanol	$(\text{C}_6\text{H}_5)_3\text{CH}$	triphenylmethane
urea*	H_2NCONH_2	urea
carbamide		
urethan	$\text{H}_2\text{NCO}_2\text{C}_2\text{H}_5$	ethyl carbamate
urethane		
<i>n</i> -valeraldehyde	$\text{CH}_3(\text{CH}_2)_3\text{CHO}$	pentanal
<i>n</i> -valeric acid	$\text{CH}_3(\text{CH}_2)_3\text{CO}_2\text{H}$	pentanoic acid
vinylacetaldehyde	$\text{CH}_2=\text{CHCH}_2\text{CHO}$	3-butenal
vinylacetylene	$\text{CH}_2=\text{CHC}\equiv\text{CH}$	1-buten-3-yne
xylene		dimethylbenzene
<i>o</i> - (1,2-*)		1,2-
<i>m</i> - (1,3-*)		1,3-
<i>p</i> - (1,4-*)		1,4-
2,3-xylylamine*		2,3-dimethylphenylamine
2,3-xylylidine ^{CA}		
2,3-dimethylaniline		



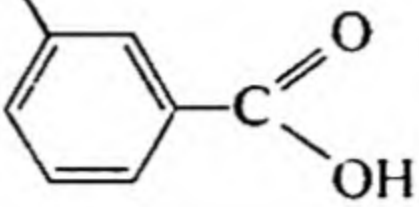
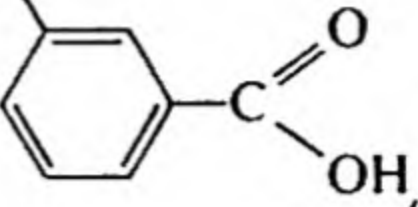
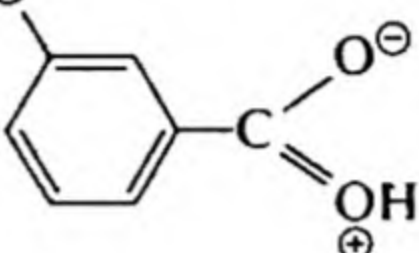
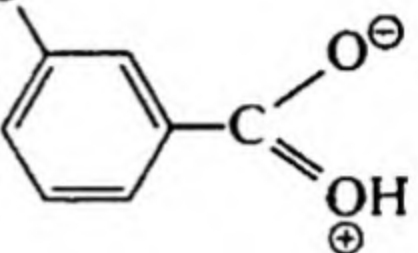
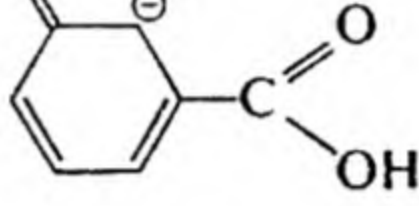
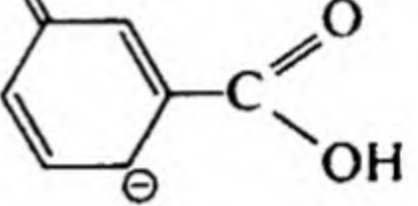
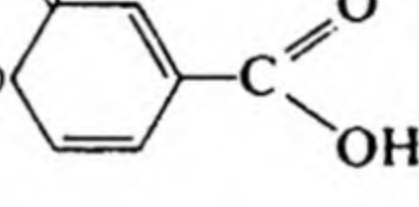
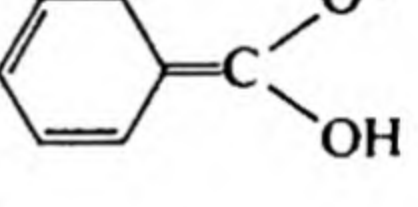
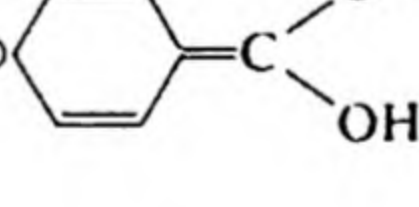
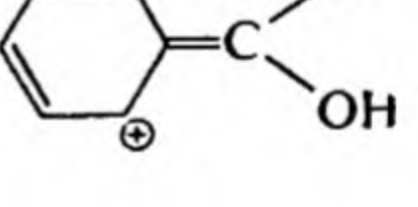
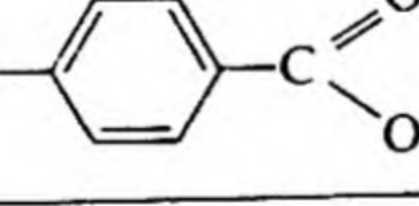
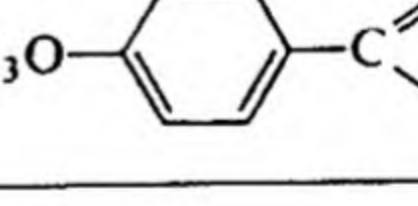
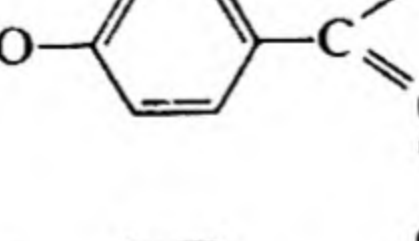
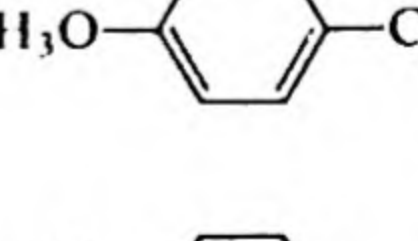
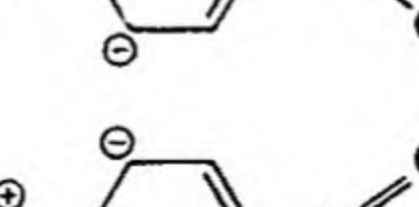



Answers to Selected Questions and Problems

Page Number	Question Number	Answer
90	10	M.W. = 174 g./mole. $C_9H_{19}F$ The arrangement of the carbon skeleton needs to be established.
90	13	<div style="display: flex; justify-content: space-around; align-items: flex-end;"> <div style="text-align: center;">  <p>OH locked in equatorial position <i>t</i>-Butyl groups must be equatorial</p> </div> <div style="text-align: center;">  <p>OH locked in axial position</p> </div> </div>
113	1d	$ \begin{array}{c} \text{H} \\ \\ \text{CH}_3\text{CH}_2-\text{C}-\text{CH}_3 \\ \\ \text{CH}_3 \end{array} $ <p>2-methylbutane</p>
113	1g	$\text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_2\text{CH}_3$ 3-hexene
113	1k	$ \begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{C}-\text{CH}_2\text{CHCH}_3 \\ \quad \\ \text{CH}_3 \quad \text{CH}_3 \end{array} $ <p>2,2,4-trimethylpentane</p>
113	2a	2-Methyl-3-ethylpentane
113	2f	2-Pentene-4-yne
113	3b	$ \begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \quad \\ \text{CH}_3\text{C}-\text{CH}-\text{C}-\text{CH}_2\text{CH}_2\text{CH}_3 \\ \quad \quad \\ \text{CH}_3 \quad \text{CH}_2\text{CH}_3 \quad \text{CH}(\text{CH}_3)_2 \end{array} $
113	3d	$ \begin{array}{c} \text{CH}_3\text{CH}=\text{CCH}_2\text{CH}_3 \\ \\ \text{CH}_3 \end{array} $

Page Number	Question Number	Answer
113	4a	Incorrect. $\text{CH}_3\text{CH}_2\text{CHCH}_3$ is 3-methylpentane. $\begin{array}{c} \\ \text{CH}_2 \\ \\ \text{CH}_3 \end{array}$
113	4c	Correct.
113	4f	Incorrect. Use number, not Greek letter. $\text{CH}_3\text{CH}_2\text{CHCH}_2\text{CH}=\text{O}$ is 3-bromopentanal. $\begin{array}{c} \\ \text{Br} \end{array}$
113	4g	Incorrect. Amine is only function and should be a suffix. <i>N,N</i> -diethylphenylamine.
114	5c	<i>tert</i> -butyl (common and IUPAC) also 1,1-dimethylethyl (IUPAC rules)
114	5d	<i>sec</i> -butyl (common and IUPAC) also 1-methylpropyl (IUPAC rules)
114	5h	β -phenethyl or β -phenylethyl (common) 2-phenylethyl (IUPAC)
114	5k	<i>n</i> -butyryl (common) butanoyl (IUPAC)
114	5l	formyl (common and IUPAC prefix name) -carbaldehyde (IUPAC suffix name)
114	6a	<i>cis-trans</i>
114	6c	Positional
115	6e	Skeletal
115	6g	<i>cis-trans</i>
115	8a	<div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="text-align: center;"> $\text{CH}_3\text{COCH}_2\text{CH}_3$ $\begin{array}{c} \\ \text{O} \end{array}$ ethyl acetate oxygen between two 2-carbon chains </div> <div style="text-align: center;"> $\text{CH}_3\text{CH}_2\text{CCH}_3$ $\begin{array}{c} \\ \text{O} \end{array}$ methyl ethyl ketone single 4-carbon chain </div> </div>
115	8c	<div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="text-align: center;"> $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{COCH}_3$ $\begin{array}{c} \\ \text{O} \end{array}$ methyl <i>n</i>-valerate carbonyl on 5-carbon chain, oxygen between carbonyl and methyl </div> <div style="text-align: center;"> $\text{CH}_3\text{COCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ $\begin{array}{c} \\ \text{O} \end{array}$ <i>n</i>-butyl acetate methyl directly on carbonyl </div> </div>
115	8e	<div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="text-align: center;"> $\text{CH}_3\text{CH}_2\text{CCl}$ $\begin{array}{c} \\ \text{O} \end{array}$ propionyl chloride chlorine on carbonyl, no hydroxy </div> <div style="text-align: center;"> $\text{Cl}-\text{CH}_2\text{CH}_2\text{COH}$ $\begin{array}{c} \\ \text{O} \end{array}$ β-chloropropionic acid chlorine at end of molecule farthest from carboxyl, which includes hydroxy </div> </div>
115	10a	2,5,7-bicyclo[2.2.2]octatriene

Page Number	Question Number	Answer
115	10b	Pentacyclo[4.2.0.0 ^{2,5} .0 ^{3,8} .0 ^{4,7}]octane
129	7	Alcohols have unshared electron pairs which can be protonated. No neutralization is a simple proton transfer from solvent conjugate cation to solvent conjugate anion, whereas this reaction involves a displacement of a group covalently bound to carbon.
136	2c	$\text{CH}_3\text{CH}=\text{CHCH}_3 + \text{H}_2\text{SO}_4 \xrightarrow{\text{(conc.)}} \text{CH}_3\text{CH}_2\underset{\text{CH}_3}{\text{CH}}-\text{OSO}_3\text{H}$
136	2h	NR
137	2k	
137	2n	$\text{CH}_3\underset{\text{O}}{\underset{\parallel}{\text{C}}}\text{CH}_2\text{CH}_3 + \text{H}_2 \xrightarrow{\text{cat.}} \text{CH}_3\underset{\text{OH}}{\underset{ }{\text{CH}}}\text{CH}_2\text{CH}_3$
137	7b	KMnO ₄ solution: cyclopentane, ethylcyclopropane NR; 1-pentene → brown ppt. $3\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{CH}_3 + 2\text{MnO}_4^- + 2\text{H}_2\text{O} \rightarrow 3\text{HOCH}_2\underset{\text{OH}}{\underset{ }{\text{CH}}}\text{CH}_2\text{CH}_2\text{CH}_3 + 2\text{MnO}_2 + 2\text{OH}^-$ Br ₂ in CCl ₄ : cyclopentane NR in dark; ethylcyclopropane decolorizes red bromine. $\text{CH}_3\text{CH}_2-\triangle + \text{Br}_2 \rightarrow \text{CH}_3\text{CH}_2-\underset{\text{Br}}{\underset{ }{\text{CH}}}\text{CH}_2\text{CH}_2\text{Br}$ and $\text{CH}_3\text{CH}_2-\triangle + \text{Br}_2 \rightarrow \text{CH}_3\text{CH}_2-\underset{\text{CH}_2\text{Br}}{\underset{ }{\text{CH}}}-\text{CH}_2\text{Br}$
137	7p	NaOH solution, boil: benzamide gives ammonia odor, vapor turns moist red litmus blue; 3,4-xylylamine no change. $\text{C}_6\text{H}_5\underset{\text{O}}{\underset{\parallel}{\text{C}}}\text{NH}_2 + \text{OH}^- \xrightarrow{\Delta} \text{C}_6\text{H}_5\text{CO}_2^- + \text{NH}_3(\text{g})$
178	12d	

Page Number	Question Number	Answer
178	15	$\text{R}-\underset{\text{O}}{\underset{\parallel}{\text{C}}}-\underset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{R} + \text{H}_2\text{O} \rightarrow 2 \underset{\text{O}}{\underset{\parallel}{\text{R}}}\text{COH},$ <p>known not to have O between R and CO. Ease of reaction suggests cleavage in $\underset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{O}-\underset{\text{O}}{\underset{\parallel}{\text{C}}}$ system, not R—O—CO system as in esters.</p> $\underset{\text{O}}{\underset{\parallel}{\text{R}}}\text{CCl} + \text{RCO}_2^- \rightarrow \underset{\text{O}}{\underset{\parallel}{\text{R}}}\text{COCR} + \text{Cl}^-$ <p>(no O between R and CO).</p> <p>Logical step in reaction is for O of $\text{RC} \begin{smallmatrix} \text{O} \\ \parallel \\ \ominus \end{smallmatrix}$ to attack C=O of RCOCl and form $\text{R}-\underset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{O}$ system without separation of R and CO.</p>
196	3	Carboxylic acids hydrogen bond at two points in the molecule, hence the dimers are more stable than those from alcohols, which have only one hydrogen bond between any two molecules. Thus, more energy and higher temperatures are required to dissociate carboxylic acid molecules by boiling. Hydrocarbons have no hydrogen bonding, hence the smallest intermolecular forces and the lowest boiling points at a given molecular weight of the three kinds of species.
224	2a	Diffuoroacetic acid > fluoracetic acid > acetic acid
224	2c	Pentane-1-sulfonic acid > pentane-1-sulfinic acid > <i>n</i> -amyl mercaptan
224	3a	<i>n</i> -Butylamine > ammonia > aniline
224	3b	Aniline > <i>p</i> -chloroaniline > <i>p</i> -nitroaniline
224	5a	$2 \text{HC}\equiv\text{CH} + 2 \text{Na} \xrightarrow[\text{solution}]{\text{liquid NH}_3} 2 (\text{HC}\equiv\text{C}:\text{Na}^+) + \text{H}_2$
224	5f	$\text{CaCO}_3 + 2 \text{CH}_3\text{COOH} \rightarrow (\text{CH}_3\text{CO}_2)_2\text{Ca} + \text{CO}_2 + \text{H}_2\text{O}$
224	5k	$6 (\text{CH}_3)_2\text{CHOH} + 2 \text{Al} \xrightarrow[\text{anhydrous 2-propanol}]{\text{amalgamated Al}} 2 [(\text{CH}_3)_2\text{CHO}]_3\text{Al} + 3 \text{H}_2$
224	6	Sodium phenoxide, calcium acetate, sodium benzenesulfonate, potassium phthalimide and sodium ethyl sulfide (provided some sodium hydroxide is added). All others decompose in water. Even sodium ethyl sulfide is extensively hydrolyzed in water without added alkali

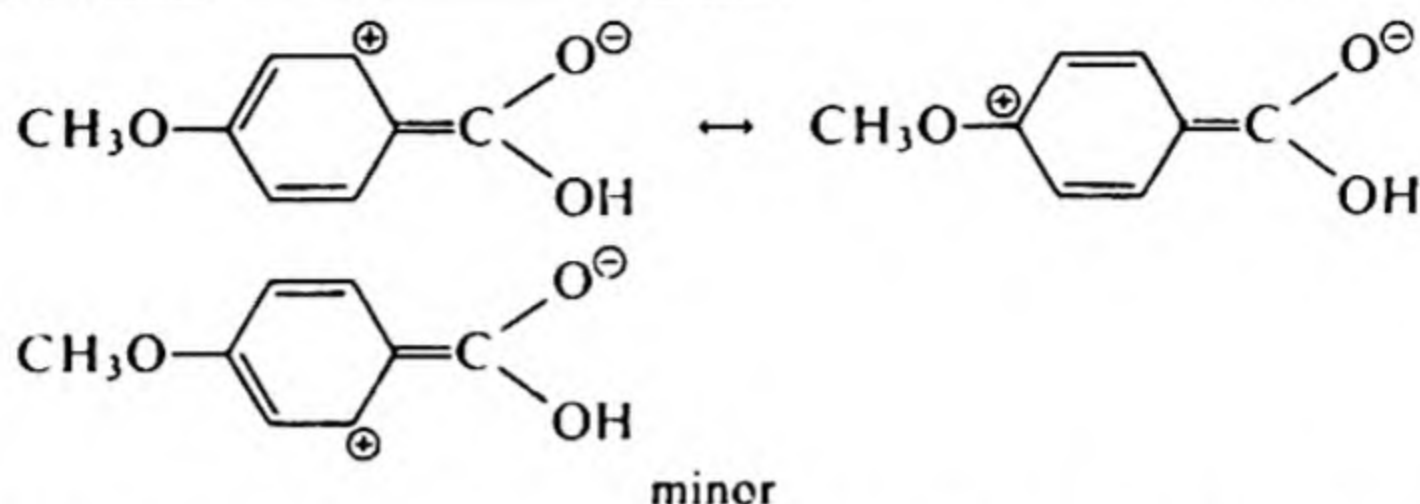
Page Number	Question Number	Answer
225	8a	<p> CH_3O  \longleftrightarrow  \longleftrightarrow </p> <p style="text-align: center;">major</p> <p> CH_3O  \longleftrightarrow  \longleftrightarrow </p> <p> CH_3O^+  \longleftrightarrow  \longleftrightarrow </p> <p> CH_3O^+  \longleftrightarrow  \longleftrightarrow </p> <p> CH_3O  \longleftrightarrow  \longleftrightarrow </p> <p style="text-align: center;">minor</p> <p> CH_3  \longleftrightarrow  \longleftrightarrow </p> <p style="text-align: center;">major</p> <p> CH_3O  \longleftrightarrow  \longleftrightarrow </p> <p> CH_3O^+  \longleftrightarrow  \longleftrightarrow </p> <p> CH_3O^+  \longleftrightarrow  \longleftrightarrow </p>

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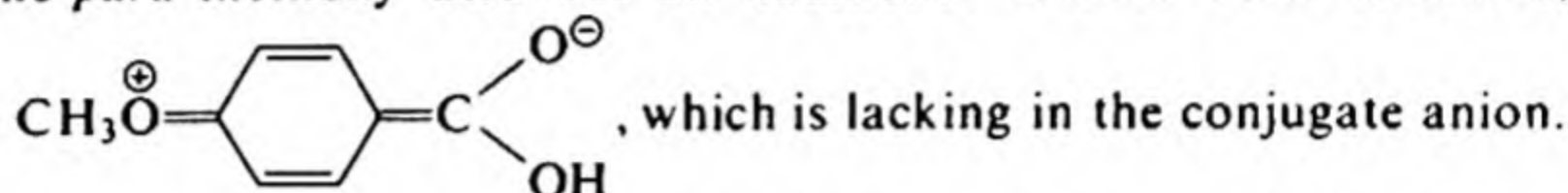
Question
Number

Answer

225 8a
(continued)



225 8b The *para* methoxy acid has an additional valence bond structure,



This means that the *para* acid is better resonance stabilized compared with its conjugate anion than benzoic acid is with respect to benzoate ion, and anisic acid is therefore weaker than benzoic acid. This valence bond structure (or one corresponding to it) is impossible in the *meta* methoxy acid, so that the *meta* acid is no better stabilized, compared to its conjugate anion, than benzoic acid. To the contrary, the inductive electron-withdrawing effect of the methoxy group tends to stabilize the *m*-methoxybenzoate ion compared with benzoate ion, and *m*-methoxybenzoic acid is therefore stronger than benzoic acid.

225 9

$$K_{\text{eq.}} = \frac{[\text{HZ}][\text{Y}^-]}{[\text{HY}][\text{Z}^-]}$$

$$K_a \text{ for HY} = \frac{[\text{H}^+][\text{Y}^-]}{[\text{HY}]}$$

$$K_a \text{ for HZ} = \frac{[\text{H}^+][\text{Z}^-]}{[\text{HZ}]}$$

$$K_{\text{eq.}} = \frac{K_a \text{ for HY}}{K_a \text{ for HZ}} = 100$$

Let $x = [\text{HZ}] = [\text{Y}^-]$ at equilibrium

$n = \text{initial } [\text{HY}] = \text{initial } [\text{Z}^-]$

$n - x = [\text{Z}^-] = [\text{HY}]$ at equilibrium

$$\frac{x^2}{(n - x)^2} = 100; \quad \frac{x}{n - x} = 10$$

$$x = 10n - 10x$$

$$11x = 10n$$

$$\frac{x}{n} = \frac{10}{11} = \text{fraction reacted}$$

As n does not appear in the answer, the fraction is independent of absolute concentrations in the absence of special solvent effects, and dilution has no effect on the position of equilibrium.

Page Number	Question Number	Answer
225	12	
282	7a	$\text{CH}_3(\text{CH}_2)_7\text{Br} \xrightarrow{\text{NaCN}^-} \text{CH}_3(\text{CH}_2)_7\text{CH} \xrightarrow[\text{H}_2\text{O}]{\text{H}^+}$ $\text{CH}_3(\text{CH}_2)_7\text{CO}_2\text{H} \xrightarrow{\text{NaHCO}_3} \text{CH}_3(\text{CH}_2)_7\text{CO}_2(\text{CH}_2)_7\text{CH}_3$
282	8b	Strong base gives elimination to form propylene oxide. This can be avoided by use of dilute aqueous sodium hydroxide (3 M or less).
282	8c	<p>$\text{CH}_3\text{CHBrCH}_2\text{CO}_2\text{H}$ shows a very strong tendency to eliminate HBr to form crotonic acid even in the most dilute aqueous base. The use of a silver oxide suspension to neutralize hydrobromic acid and to promote removal of bromide ion to form a carbonium ion may be successful in effecting some of the desired displacement.</p> $\text{CH}_3\text{CHBrCH}_2\text{CO}_2\text{H} \xrightarrow{\text{H}_2\text{O} + \text{Ag}_2\text{O}}$ $\text{CH}_3\underset{\text{OH}}{\text{CH}}\text{CH}_2\text{CO}_2\text{H} + \text{AgBr}$
291	2a	An aryl halide cannot be prepared by displacement of a phenolic hydroxy group no matter what reagent is used. The carbon-oxygen bond is too well resonance stabilized.
291	2c	The desired cleavage can be effected in time by boiling under reflux. However, use of anhydrous hydrogen bromide to provide a higher bromide ion concentration or of hydrogen iodide to provide a more nucleophilic displacing agent would make the reaction easier for primary alkyl ethers.
291	3a	$\text{CH}_3\text{CH}_2\text{CHOHCH}_3 + \text{HCl} \xrightarrow[\text{(conc.)}]{\text{ZnCl}_2}$ $\text{CH}_3\text{CH}_2\text{CHClCH}_3 + \text{H}_2\text{O}$

Page Number	Question Number	Answer
291	3c	$\text{Ph}_2\text{C}(\text{OH})-\text{C}(\text{OH})\text{Ph}_2 \xrightarrow[\Delta]{\text{H}^+} \text{Ph}_3\text{C}-\text{C}(=\text{O})\text{Ph} + \text{H}_2\text{O}$
291	3d	$(\text{C}_2\text{H}_5)_3\text{CCHOHCH}_3 \xrightarrow[\Delta]{\text{H}_2\text{SO}_4} (\text{C}_2\text{H}_5)_2\text{C}=\text{C}(\text{CH}_3)\text{C}_2\text{H}_5 + \text{H}_2\text{O}$
291	4a	$\text{CH}_3(\text{CH}_2)_4\text{OH} \xrightarrow[\text{HBr} + \text{H}_2\text{SO}_4]{\text{PBr}_3 \text{ or}} \text{CH}_3(\text{CH}_2)_4\text{Br}$
292	4d	$(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{OH} \xrightarrow[\text{HBr} + \text{H}_2\text{SO}_4]{\text{PBr}_3 \text{ or}} (\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ $\xrightarrow{\text{Na}} (\text{CH}_3)_2\text{CH}(\text{CH}_2)_4\text{CH}(\text{CH}_3)_2$
292	4h	$\text{CH}_3\text{O}-\text{C}_6\text{H}_3(\text{OCH}_3)-\text{CHO} \xrightarrow[\text{conc. HBr}]{\text{conc. HI or}} \text{HO}-\text{C}_6\text{H}_3(\text{OH})-\text{CHO}$
292	5	$\text{H}_2\text{SO}_4 + 2\text{HBr} \rightleftharpoons \text{H}_2\text{SO}_3 + \text{Br}_2 + \text{H}_2\text{O}$ $\text{CH}_3(\text{CH}_2)_3\text{OH} \xrightarrow{\text{HBr}} \text{CH}_3(\text{CH}_2)_3\text{Br} \text{ main product}$ <div style="margin-left: 40px;"> $\begin{array}{l} \xrightarrow{\text{H}^+} \text{CH}_3(\text{CH}_2)_3\text{O}(\text{CH}_2)_3\text{CH}_3 \\ \xrightarrow[\text{(oxidation)}]{\text{H}_2\text{SO}_4 \text{ or } \text{Br}_2} \text{CH}_3(\text{CH}_2)_2\text{CHO} \xrightarrow{\text{Br}_2} \text{CH}_3\text{CH}_2\text{CHBrCHO} \\ \xrightarrow{\text{elimination}} \text{CH}_3\text{CH}_2\text{CH}=\text{CH}_2 \begin{array}{l} \xrightarrow{\text{HBr}} \text{CH}_3\text{CH}_2\text{CHBrCH}_3 \\ \xrightarrow[\text{addition}]{\text{H}^+, \text{H}_2\text{O}} \text{CH}_3\text{CH}_2\text{CHOHCH}_3 \\ \xrightarrow[\text{addition}]{\text{H}_2\text{SO}_4} \text{CH}_3\text{CH}_2\text{CH}(\text{OSO}_3\text{H})\text{CH}_3 \end{array} \\ \xrightarrow[\text{(esterification)}]{\text{H}_2\text{SO}_4} \text{CH}_3(\text{CH}_2)_3\text{OSO}_3\text{H} \end{array}$ <p>(These can also be formed from $\text{CH}_3(\text{CH}_2)_3\text{OH}$ via carbonium ion rearrangements.)</p> </div>
292	6	<p>Side reactions corresponding to all those in Question 5 will occur, with somewhat more emphasis on the eliminations and rearrangements. In addition, skeletal rearrangement may occur.</p> $(\text{CH}_3)_2\text{CHCH}_2\text{OH} \xrightarrow{\text{H}^+} \xrightarrow{-\text{H}_2\text{O}} (\text{CH}_3)_2\text{CHCH}_2^+ \rightarrow$

Page Number	Question Number	Answer
292 (continued)	6	$\text{CH}_3\overset{\oplus}{\text{C}}\text{HCH}_2\text{CH}_3 \begin{cases} \xrightarrow{\text{Br}^-} \text{CH}_3\text{CHBrCH}_2\text{CH}_3 \\ \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{CHOHCH}_2\text{CH}_3 \\ \xrightarrow{\text{HSO}_4^-} \text{CH}_3\underset{\text{OSO}_3\text{H}}{\text{CH}}\text{CH}_2\text{CH}_3 \\ \xrightarrow{-\text{H}^+} \text{CH}_3\text{CH}=\text{CHCH}_3 \end{cases}$
337	3a	$\text{CH}_2=\text{CHCH}=\text{CHCH}_3 + \text{HBr} \xrightarrow{\text{peroxide}}$ $[\text{BrCH}_2\overset{\delta\cdot}{\text{C}}\text{H}\cdots\text{CH}\cdots\overset{\delta\cdot}{\text{C}}\text{HCH}_3] \rightarrow$ $\left. \begin{array}{l} \text{BrCH}_2\text{CH}_2\text{CH}=\text{CHCH}_3 \\ \text{and } \text{BrCH}_2\text{CH}=\text{CHCH}_2\text{CH}_3 \end{array} \right\} \text{mainly}$ $\text{CH}_2=\text{CHCH}=\text{CHCH}_3 + \text{HBr} \xrightarrow{\text{peroxide}}$ $[\overset{\delta\cdot}{\text{C}}\text{H}_2\cdots\text{CH}\cdots\overset{\delta\cdot}{\text{C}}\text{HCHBrCH}_3] \rightarrow$ $\left. \begin{array}{l} \text{CH}_3\text{CH}=\text{CHCHBrCH}_3 \\ \text{and } \text{CH}_2=\text{CHCH}_2\text{CHBrCH}_3 \end{array} \right\} \text{in smaller amounts}$
337	3b	$\text{CH}_3=\text{CHCH}=\text{CHCH}_3 + \text{HBr} \xrightarrow{\text{inhibitor}}$ $[\text{CH}_3\overset{\delta+}{\text{C}}\text{H}\cdots\text{CH}\cdots\overset{\delta+}{\text{C}}\text{HCH}_3] + \text{Br}^- \rightarrow$ $\text{CH}_3\text{CH}=\text{CHCHBrCH}_3 \text{ mainly}$ $\text{CH}_2=\text{CHCH}=\text{CHCH}_3 + \text{HBr} \xrightarrow{\text{inhibitor}}$ $[\overset{\delta+}{\text{C}}\text{H}_2\cdots\text{CH}\cdots\overset{\delta+}{\text{C}}\text{HCH}_2\text{CH}_3] + \text{Br}^- \rightarrow$ $\left. \begin{array}{l} \text{BrCH}_2\text{CH}=\text{CHCH}_2\text{CH}_3 \\ \text{and } \text{CH}_2=\text{CHCHBrCH}_2\text{CH}_3 \end{array} \right\} \text{in smaller amounts}$
337	3c	$\text{CH}_3\text{CH}=\text{CHCH}_3 + \text{Cl}_2 \xrightarrow{350^\circ} \text{CH}_3\text{CH}=\text{CHCH}_2\text{Cl} + \text{HCl} \text{ or}$ $\text{CH}_3\text{CH}=\text{CHCH}_3 + 2\text{Cl}_2 \xrightarrow{350^\circ} \text{ClCH}_2\text{CH}=\text{CHCH}_2\text{Cl} + 2\text{HCl}$
337	4a	$\text{CH}_3\text{CH}=\text{CH}_2 \xrightarrow[\text{peroxide}]{\text{HBr}} \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \xrightarrow{\text{NaCN}} \text{CH}_3(\text{CH}_2)_2\text{CN}$
337	4b	$\text{C}_6\text{H}_5\text{CH}_3 \xrightarrow[\text{light}]{\text{Cl}_2} \text{C}_6\text{H}_5\text{CH}_2\text{Cl} \xrightarrow[\text{excess}]{\text{NH}_3} \text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$

Page Number	Question Number	Answer
337	5a and c	<p>I. $(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{Cl}$ $3 \times 1.0 = 3.0$</p> <p>II. $(\text{CH}_3)_2\text{CHCHClCH}_3$ $2 \times 4.3 = 8.6$</p> <p>III. $(\text{CH}_3)_2\text{CClCH}_2\text{CH}_3$ $1 \times 7.0 = 7.0$</p> <p>IV. $\text{ClCH}_2\text{CHCH}_2\text{CH}_3$ $6 \times 1.0 = 6.0$</p> <p style="margin-left: 100px;"> </p> <p style="margin-left: 100px;">CH_2</p> <p>I:II:III:IV = 3.0:8.6:7.0:6.0 at 100°</p>
394	1	<p>(1) $\text{R}-\text{C} \begin{array}{c} \curvearrowright \text{y} \\ \parallel \\ \text{b} \end{array} \rightarrow \text{R}-\text{C}^{\oplus} \equiv \text{b} + \text{:y}^-$</p> <p>Ionization, including electron release by b as the leaving group, y, takes an electron pair.</p> <p>(2) $\text{R}-\text{C} \begin{array}{c} \text{y} \\ \parallel \\ \text{b} \end{array} + \text{H}^+ = \text{R}-\text{C} \begin{array}{c} \text{y} \\ \parallel \\ \text{bH}^{\oplus} \end{array}$</p> <p>Protonation of b to make a more electrophilic species.</p> <p>(3) $\text{R}-\text{C} \begin{array}{c} \text{y} \\ \parallel \\ \text{b} \end{array} + \text{:z}^- \rightarrow \text{R}-\text{C} \begin{array}{c} \text{z} \\ \\ \text{y} \\ \\ \text{b}^{\ominus} \end{array}$</p> <p>Addition of a nucleophile to the electrophilic carbon atom with corresponding electron release from carbon to the electronegative atom, b.</p> <p>(4) $\text{R}-\text{C} \begin{array}{c} \text{y} \\ \parallel \\ \text{b} \end{array} + \text{:z}^- \rightarrow \left[\text{R}-\text{C} \begin{array}{c} \text{z} \\ \vdots \\ \vdots \\ \vdots \\ \parallel \\ \text{b} \end{array} \cdots \text{y} \right] \rightarrow \text{R}-\text{C} \begin{array}{c} \text{z} \\ \parallel \\ \text{b} \end{array} + \text{:y}^-$</p> <p>Direct displacement of leaving group y by nucleophile z (the least likely possibility, and one which would operate only when the C—y sigma orbital is much weaker than the C—b pi orbital, or very highly polarized and the C—b pi orbital very difficultly polarizable in the direction required; either combination of factors occurs only rarely, if at all).</p>
406	1a	NR
406	1b	NR
407	1c	$(\text{CH}_3\text{CH}_2)_2\text{CO} + \text{HCN} \xrightarrow{\text{CN}^-} (\text{CH}_3\text{CH}_2)_2\text{C} \begin{array}{l} \text{CN} \\ \text{OH} \end{array}$
407	1g	$\text{CH}_3\text{CH}=\text{CHCHO} + 2\text{CH}_3(\text{CH}_2)_3\text{OH} \xrightarrow[\text{CaCl}_2]{\text{H}^+}$ $\text{CH}_3\text{CH}=\text{CHCH}(\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2 + \text{H}_2\text{O}$

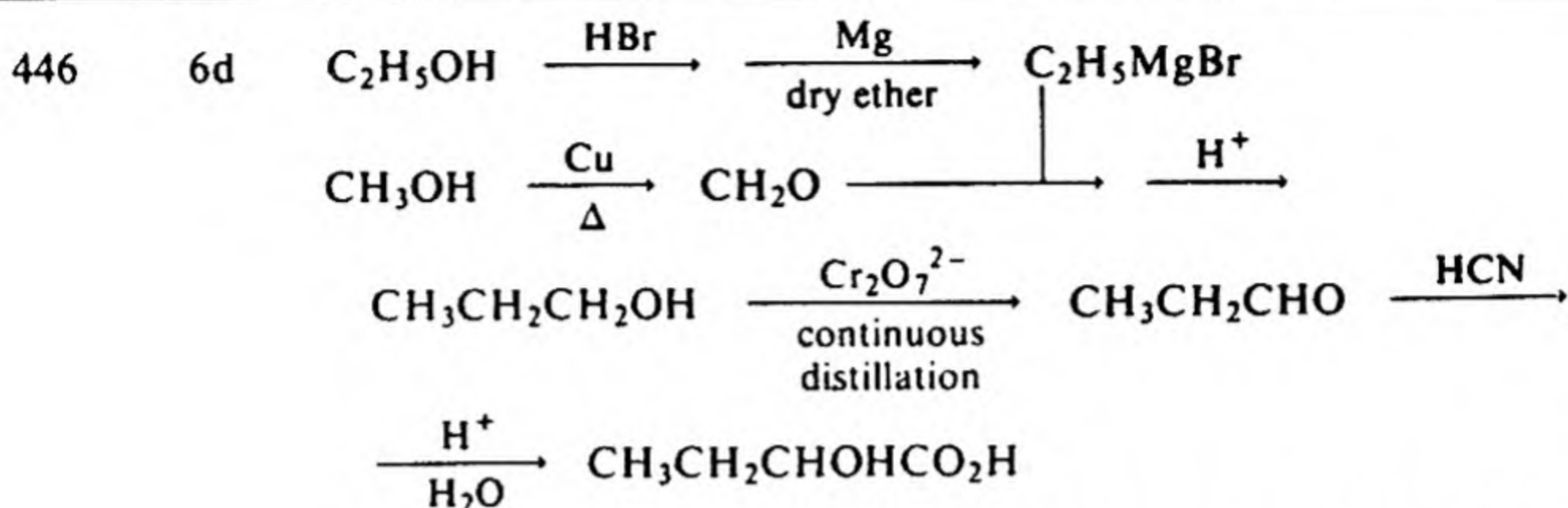
Page Number	Question Number	Answer
407	1j	$(\text{CH}_3)_2\text{C}=\text{CHCOCH}=\text{C}(\text{CH}_3)_2 + (\text{C}_2\text{H}_5\text{O})_3\text{CH} \xrightarrow{\text{H}^+}$ $[(\text{CH}_3)_2\text{C}=\text{CH}]_2\text{C}(\text{OC}_2\text{H}_5)_2 + \text{HCO}_2\text{C}_2\text{H}_5$
407	2a	$\text{CH}_3\text{CHO} \xrightarrow{\text{HCN}} \text{CH}_3\text{CHOHCN} \xrightarrow[\text{H}_2\text{O}]{\text{H}^+}$ $\text{CH}_3\text{CHOHCO}_2\text{H}$
407	2c	$\text{CH}_3\text{CHO} \xrightarrow{\text{NH}_2\text{OH}} \text{CH}_3\text{CH}=\text{NOH} \xrightarrow[\text{C}_2\text{H}_5\text{OH}]{\text{Na} +}$ $\text{CH}_3\text{CH}_2\text{NH}_2$
407	5a	$\text{CH}_3(\text{CH}_2)_2\text{CHO} \xrightarrow[\text{sat.}]{\text{NaHSO}_3} \text{CH}_3(\text{CH}_2)_2\text{CHOHSO}_3\text{Na} \xrightarrow{\text{H}^+}$ $\text{CH}_3(\text{CH}_2)_2\text{CHO}$
407	5e	$\text{H}_2\text{NC}\equiv\text{N} + \text{C}_2\text{H}_5\text{OH} \xrightarrow{\text{H}^+} \text{H}_2\text{N}-\underset{\text{NH}_2}{\overset{\oplus}{\text{C}}}-\text{OC}_2\text{H}_5 \xrightarrow[\text{Cl}^-]{\text{NH}_4^+}$ $\text{H}_2\text{N}-\underset{\text{NH}_2}{\overset{\oplus}{\text{C}}}=\text{NH}_2\text{Cl}^-$
414	3a	$\text{C}_6\text{H}_5\text{N}=\text{C}=\text{O} + 2\text{OH}^- \rightarrow \text{C}_6\text{H}_5\text{NH}_2 + \text{CO}_3^{2-}$
414	3b	NR
414	3c	$\text{CH}_3\text{CH}=\text{C}=\text{O} + \text{H}_2\text{S} \rightarrow \text{CH}_3\text{CH}_2\text{COSH}$
414	3g	$\text{S}=\text{C}=\text{S} + 2\text{C}_6\text{H}_5\text{NH}_2 \rightarrow \text{C}_6\text{H}_5\text{NHCS}^-\text{C}_6\text{H}_5\text{NH}_3^+$ $\quad \quad \quad \parallel$ $\quad \quad \quad \text{S}$
446	3d	$2\text{CH}_3\underset{\text{OH}}{\text{CH}}\text{CH}_2\text{CHCHO} + \text{AlH}_4^- \rightarrow$ $\begin{array}{c} \text{OH} \\ \\ \text{CH}_3\text{CHCH}_2\text{CH}_2 \\ \quad \\ \text{O} \quad \text{O} \\ \diagdown \quad \diagup \\ \text{Al} \\ \diagup \quad \diagdown \\ \text{O} \quad \text{O} \\ \quad \\ \text{CH}_3\text{CHCH}_2\text{CH}_2 \end{array} + \text{H}_2$ $4\text{CH}_3\underset{\text{OH}}{\text{CH}}\text{CH}_2\text{CHO} + \text{BH}_4^- \rightarrow \left(\underset{\text{OH}}{\text{CH}_3\text{CHCH}_2\text{CH}_2\text{O}} \right)_4\text{B}^-$
446	4a	$\text{CH}_3\text{CH}_2\text{CH}_2\text{OH} \xrightarrow{\text{HBr}} \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \xrightarrow[\text{dry ether}]{\text{Mg}}$ $\text{CH}_3\text{CH}_2\text{CH}_2\text{MgBr} \xrightarrow{\text{CH}_2\text{O}} \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$

Page Number	Question Number	Answer
446	4b	$\text{CH}_3\text{CH}_2\text{CH}_2\text{MgBr} \xrightarrow{\text{CH}_3\text{CHO}} \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{CH}_2\text{CH}_2\underset{\text{OH}}{\text{CH}}\text{CH}_3$ <p style="text-align: center;">(as in 4a)</p>
446	4f	$\text{CH}_3\text{CH}_2\text{CH}_2\text{MgBr} \xrightarrow{\text{C}_6\text{H}_5\text{CN}} \xrightarrow[\text{H}_2\text{O}]{\text{H}^+} \text{CH}_3\text{CH}_2\text{CH}_2\underset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{C}_6\text{H}_5$ <p style="text-align: center;">(as in 4a)</p>
446	5a	$\text{C}_6\text{H}_5\text{MgBr} + \text{C}_6\text{H}_5\text{CN} \rightarrow \text{C}_6\text{H}_5\underset{\text{NMgBr}}{\underset{\text{ }}{\text{C}}}\text{C}_6\text{H}_5$ <p style="text-align: center;">or</p> $\xrightarrow[\text{H}_2\text{O}]{\text{H}^+} \text{C}_6\text{H}_5\text{CON}(\text{CH}_3)_2 \quad \text{or} \quad (\text{C}_6\text{H}_5)_2\underset{\text{OMgBr}}{\underset{ }{\text{CN}}}(\text{CH}_3)_2$ <p style="text-align: center;">(C₆H₅)₂CO</p>
446	5c	$\text{CH}_3(\text{CH}_2)_3\text{MgBr} + \text{Naphthalene} \rightarrow \text{Naphthalene-N}=\text{C}(\text{CH}_2)_3\text{CH}_3\text{OMgBr} \xrightarrow{\text{H}_2\text{O}} \text{Naphthalene-NHCO}(\text{CH}_2)_3\text{CH}_3$
446	5d	$\text{CH}_3\text{MgI} + \text{HC}\equiv\text{CH} \rightarrow \text{HC}\equiv\text{CMgI} \xrightarrow{\text{CO}_2} \text{HC}\equiv\text{CCO}_2\text{MgI} \xrightarrow{\text{HCl}} \text{HC}\equiv\text{CCO}_2\text{H}$
446	6a	$\text{C}_2\text{H}_5\text{OH} \xrightarrow{\text{HBr}} \text{C}_2\text{H}_5\text{Br} \xrightarrow[\text{dry ether}]{\text{Mg}} \text{C}_2\text{H}_5\text{MgBr}$ <p style="text-align: center;"> </p> $\xrightarrow[\text{continuous distillation}]{\text{Cr}_2\text{O}_7^{2-}} \text{CH}_3\text{CHO} \xrightarrow{\text{H}_2\text{O}} \text{C}_2\text{H}_5\underset{\text{OH}}{\text{CH}}\text{CH}_3$
446	6b	$\text{C}_2\text{H}_5\text{OH} \xrightarrow{\text{HBr}} \xrightarrow[\text{dry ether}]{\text{Mg}} \text{C}_2\text{H}_5\text{MgBr}$ <p style="text-align: center;"> </p> $\xrightarrow[170]{\text{H}_2\text{SO}_4} \text{CH}_2=\text{CH}_2 \xrightarrow{\text{HOCl}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ <p style="text-align: center;"> </p> $\text{C}_2\text{H}_5\text{MgBr} \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ <p style="text-align: center;"> </p> $\text{ClCH}_2\text{CH}_2\text{OH} \xrightarrow[\text{(conc.)}]{\text{KOH}} \text{CH}_2\text{CH}_2\text{O}$

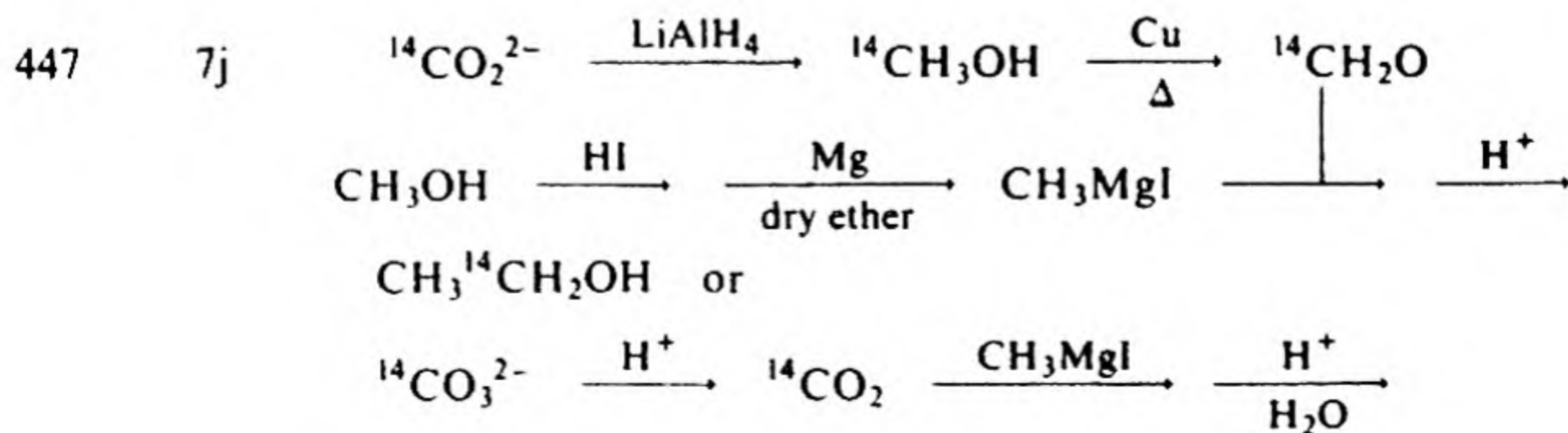
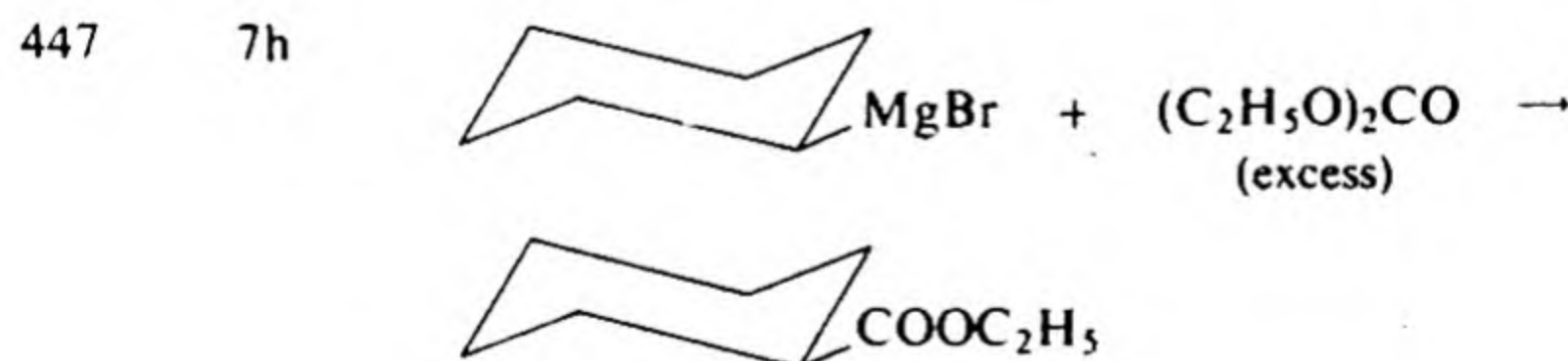
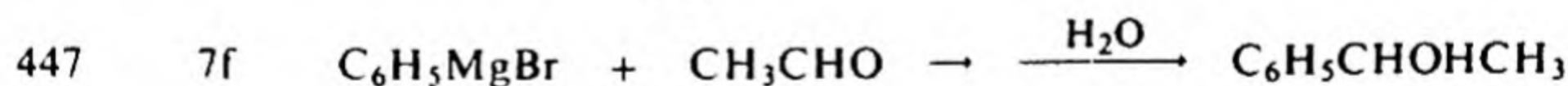
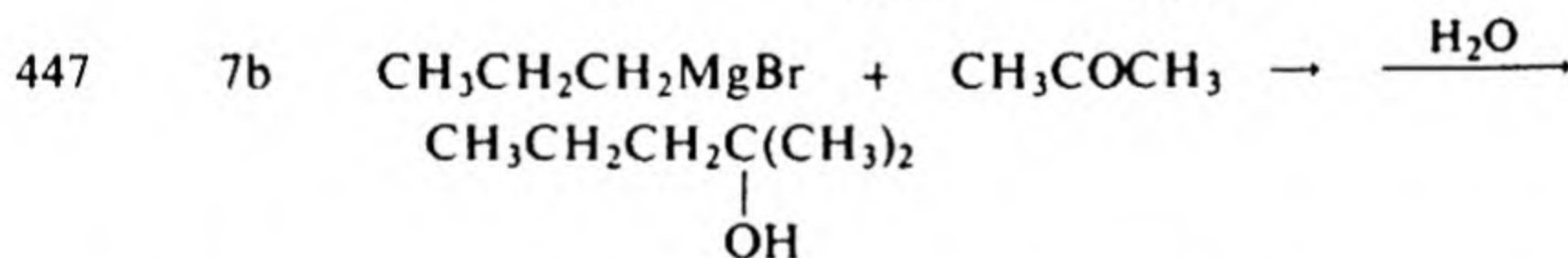
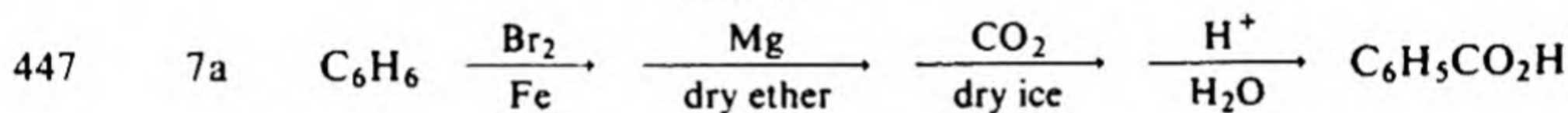
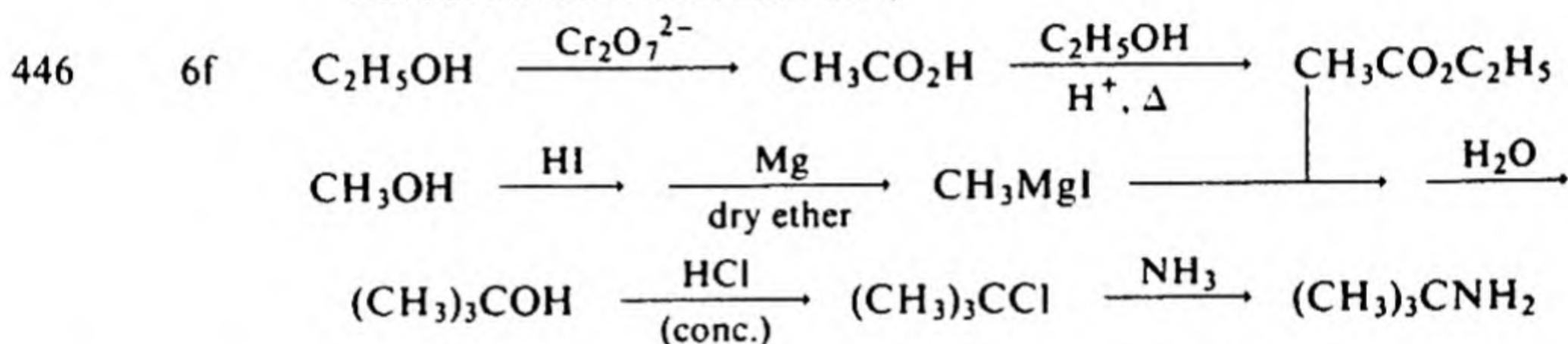
Page
Number

Question
Number

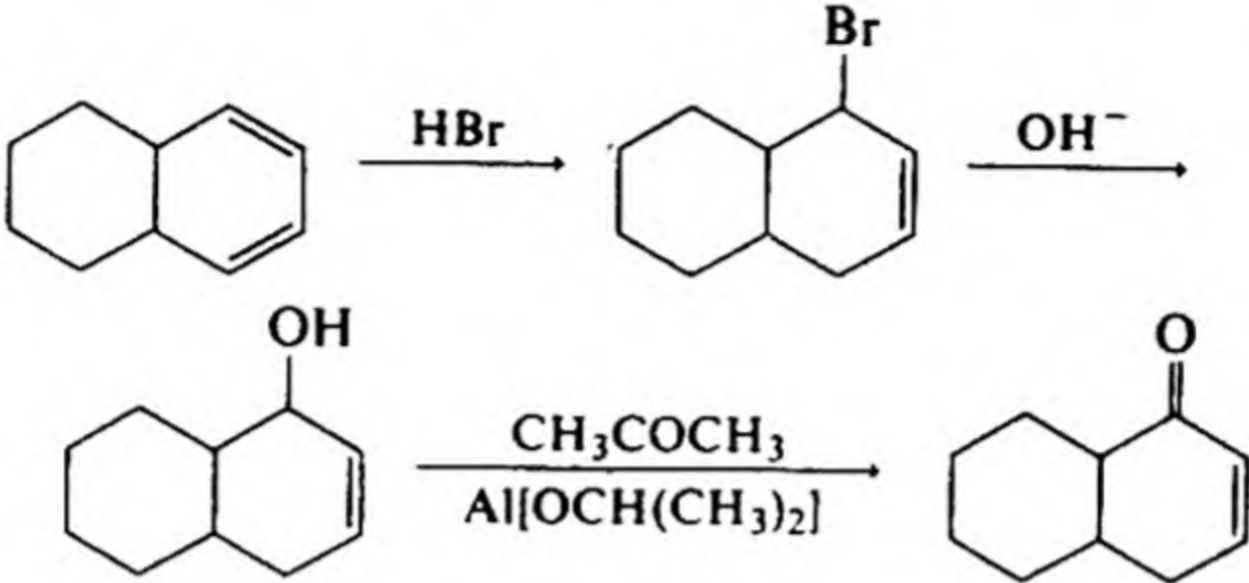
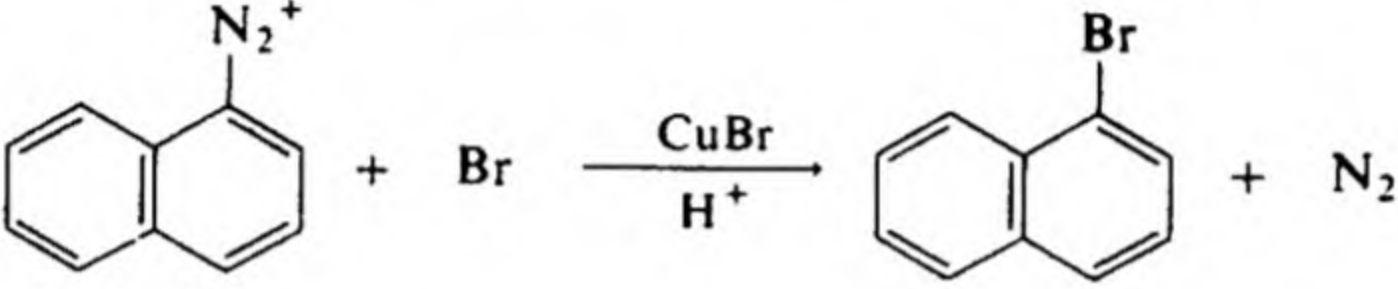
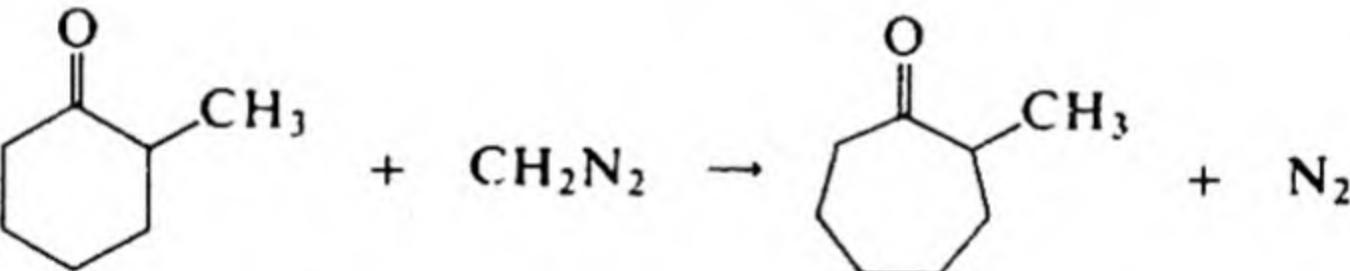
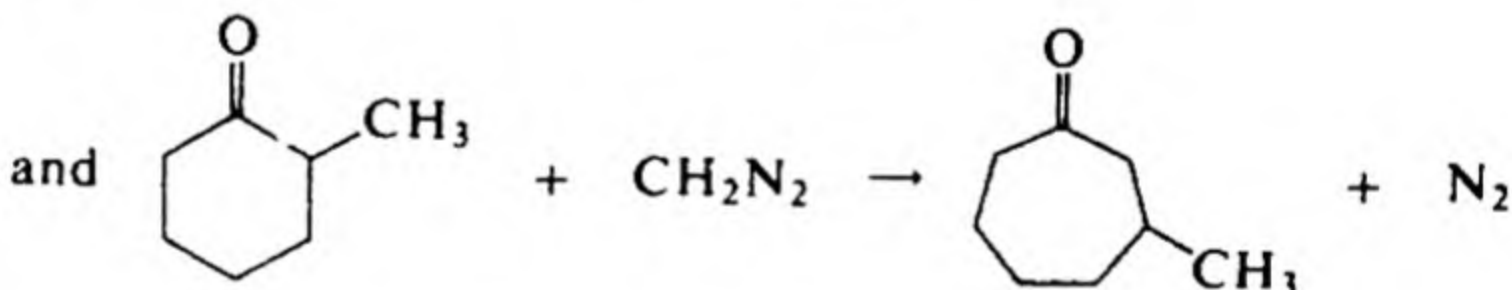
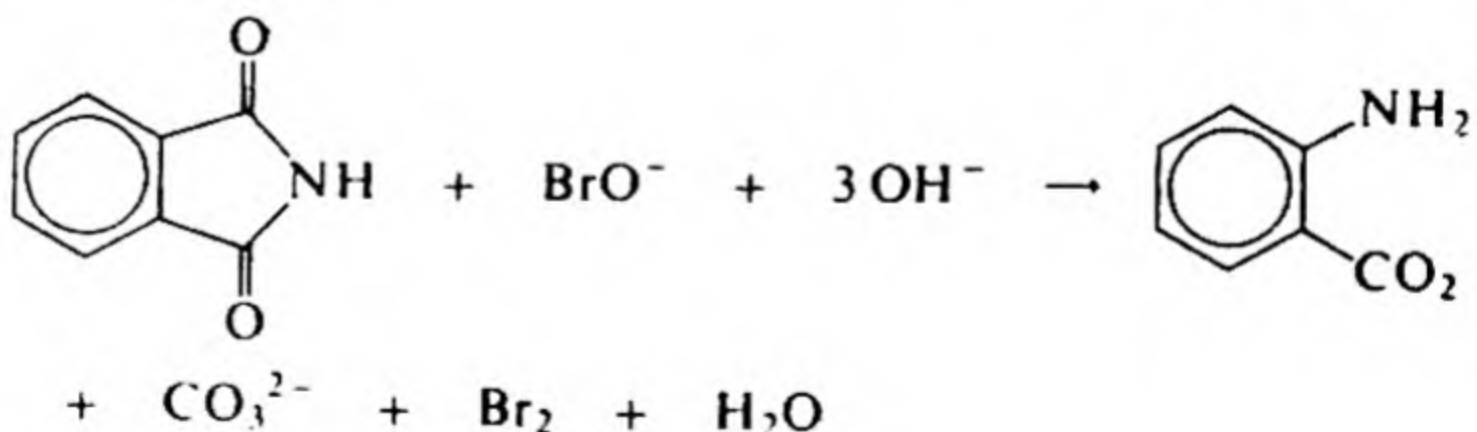
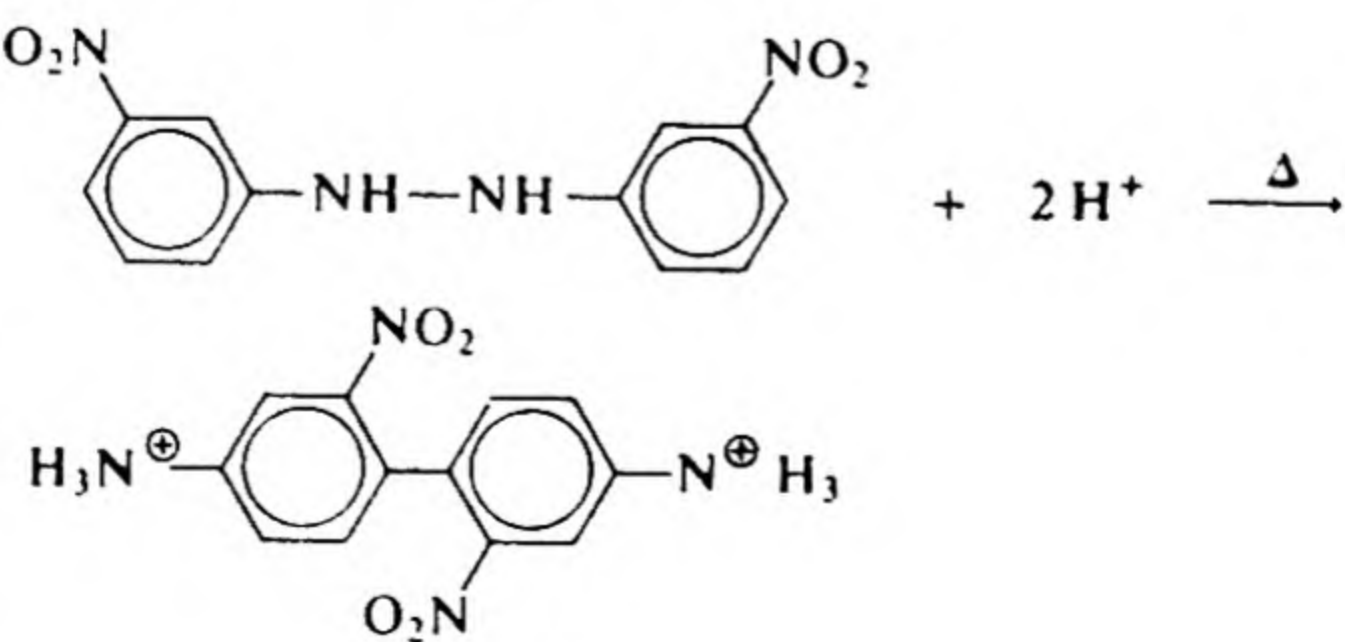
Answer



Several other methods can also be used. (Synthesis problems often have several suitable answers.)



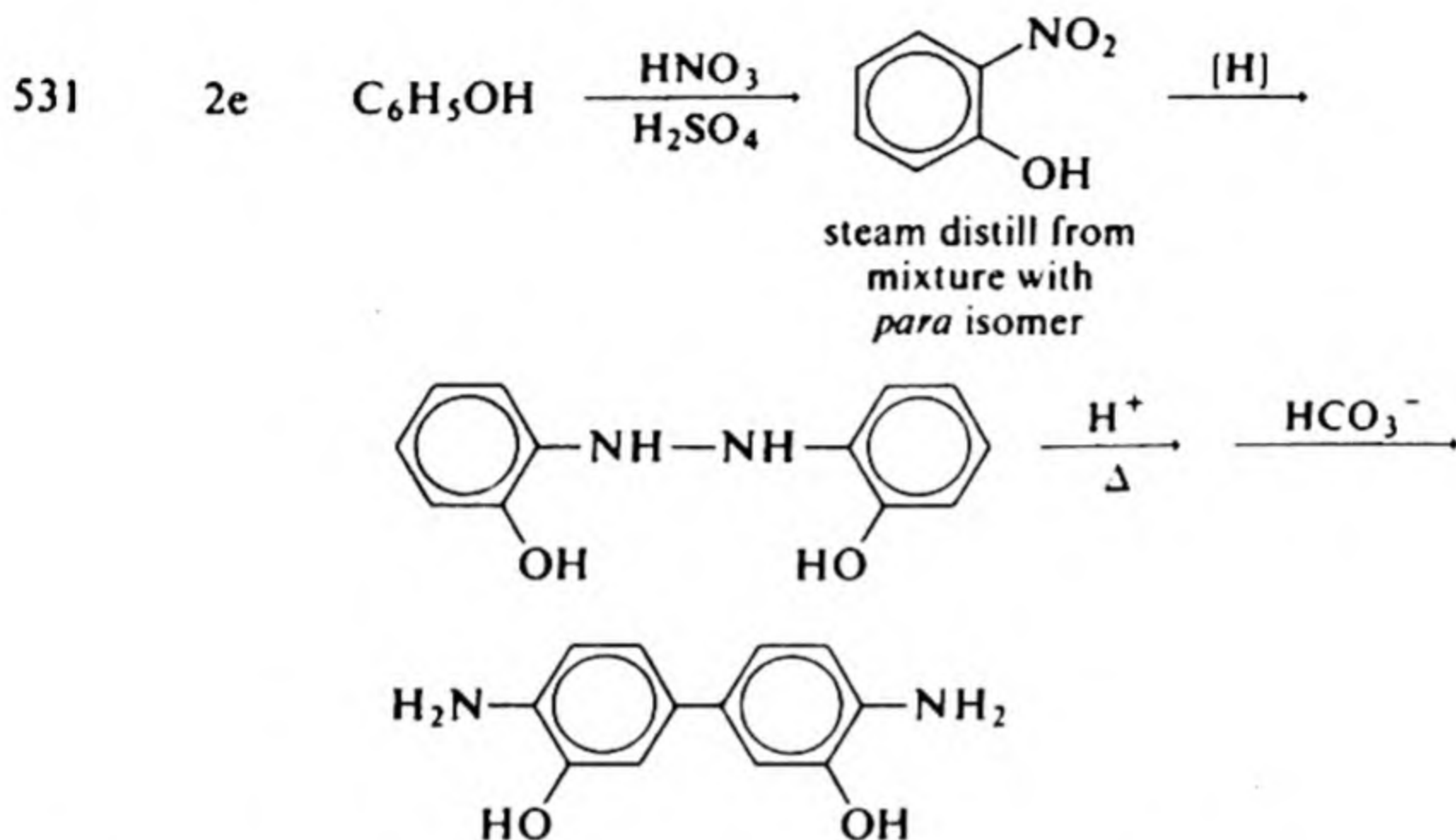
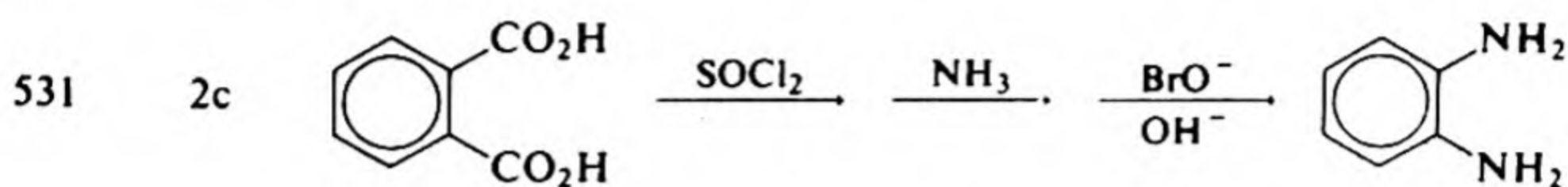
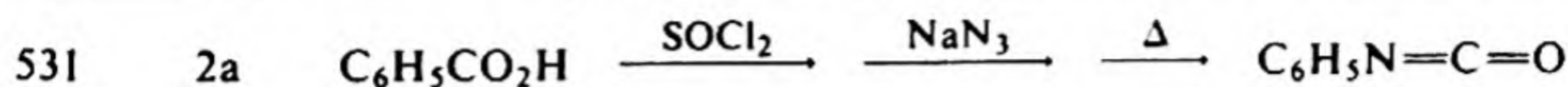
Page Number	Question Number	Answer
447 (continued)	7j	$\text{CH}_3^{14}\text{CO}_2\text{H} \xrightarrow{\text{LiAlH}_4} \xrightarrow{\text{H}_2\text{O}} \text{CH}_3^{14}\text{CH}_2\text{OH}$
471	6c	$\text{CH}_2(\text{CO}_2\text{C}_2\text{H}_5)_2 \xrightarrow[\text{HCl}]{\text{NaNO}_2} \text{HON}=\text{C}(\text{CO}_2\text{C}_2\text{H}_5)_2 \xrightarrow[\text{C}_2\text{H}_5\text{OH}]{\text{Na(Hg)}}$ $\text{H}_2\text{NCH}(\text{CO}_2\text{C}_2\text{H}_5)_2 \xrightarrow{\text{C}_2\text{H}_5\text{ONa}} \xrightarrow{\text{CH}_3\text{I}}$ $\text{CH}_3\underset{\text{NH}_2}{\text{C}}(\text{CO}_2\text{C}_2\text{H}_5)_2 \xrightarrow[\Delta]{\text{H}^+, \text{H}_2\text{O}} \text{CH}_3\underset{\oplus\text{NH}_3}{\text{CH}}\text{CO}_2^\ominus$
471	6f	$\text{CH}_2(\text{CO}_2\text{C}_2\text{H}_5)_2 \xrightarrow{\text{C}_2\text{H}_5\text{ONa}} \xrightarrow[\text{(S}_N2\text{)}]{\text{CH}_3\text{CHBrCH}_2\text{Br}}$ $\text{CH}_3\underset{\text{Br}}{\text{CH}}\text{CHCH}(\text{CO}_2\text{C}_2\text{H}_5)_2 \xrightarrow{\text{C}_2\text{H}_5\text{ONa}}$ $\text{CH}_3\underset{\text{CH}_2}{\text{CH}}\text{C}(\text{CO}_2\text{C}_2\text{H}_5)_2 \xrightarrow[\Delta]{\text{OH}^-} \xrightarrow[\Delta]{\text{H}^+} \text{CH}_3\underset{\text{CH}_2}{\text{CH}}-\text{CHCO}_2\text{H}$
471	7a	$\text{CH}_3\text{COCH}_2\text{CO}_2\text{C}_2\text{H}_5 \xrightarrow{\text{C}_2\text{H}_5\text{ONa}} \xrightarrow{\text{CH}_3\text{I}} \xrightarrow{\text{C}_2\text{H}_5\text{ONa}}$ $\xrightarrow{\text{CH}_3\text{I}} \text{CH}_3\text{COC}(\text{CH}_3)_2\text{CO}_2\text{C}_2\text{H}_5 \xrightarrow[\text{in C}_2\text{H}_5\text{OH}]{\text{OH}^-} \xrightarrow{\text{H}^+}$ $(\text{CH}_3)_2\text{CHCO}_2\text{H}$
471	7f	$2 \text{CH}_3\text{COCH}_2\text{CO}_2\text{C}_2\text{H}_5 \xrightarrow{\text{2 C}_2\text{H}_5\text{ONa}} \xrightarrow{\text{CH}_2\text{Br}_2}$ $\text{CH}_3\text{CO}\underset{\text{CH}_2}{\text{CH}}\text{CO}_2\text{C}_2\text{H}_5 \xrightarrow[\text{H}_2\text{O}, \Delta]{\text{H}^+} \text{CH}_3\text{CO}(\text{CH}_2)_3\text{COCH}_3$ $\text{CH}_3\text{CO}\underset{\text{CH}_2}{\text{CH}}\text{CO}_2\text{C}_2\text{H}_5$
494	2a	$\text{HC}\equiv\text{CH} \xrightarrow[\text{H}^+, \text{Hg}^{2+}]{\text{H}_2\text{O}} \text{CH}_3\text{CHO} \xrightarrow[\text{Ni}]{\text{H}_2}$ $\text{C}_2\text{H}_5\text{OH} \xrightarrow{\text{Al(Hg)}} \text{Al(OC}_2\text{H}_5)_3$ $\text{CH}_3\text{CHO} \xrightarrow{\text{Al(OC}_2\text{H}_5)_3} \text{CH}_3\text{CO}_2\text{C}_2\text{H}_5$
494	2c	$\text{C}_6\text{H}_5\text{CHO} + \text{CH}_3\text{COCH}_3 \xrightarrow{\text{OH}^-}$ $\text{C}_6\text{H}_5\text{CH}=\text{CHCOCH}=\text{CHC}_6\text{H}_5$ $\text{C}_6\text{H}_5\text{CH}=\text{CHCOCH}=\text{CHC}_6\text{H}_5 \xrightarrow{[(\text{CH}_3)_2\text{CHO}]_3\text{Al}} \xrightarrow{(\text{CH}_3)_2\text{CHOH}}$

Page Number	Question Number	Answer
494 (continued)	2c	$(C_6H_5CH=CH)_2CHOH$ $CH_3COCH_3 \xrightarrow[Ni]{H_2} (CH_3)_2CHOH \xrightarrow{Al(Hg)} [(CH_3)_2CHO]_3Al$
494	2f	
508	1a	
508	1b	 <p>and</p> 
531	1h	
531	1k	

Page
Number

Question
Number

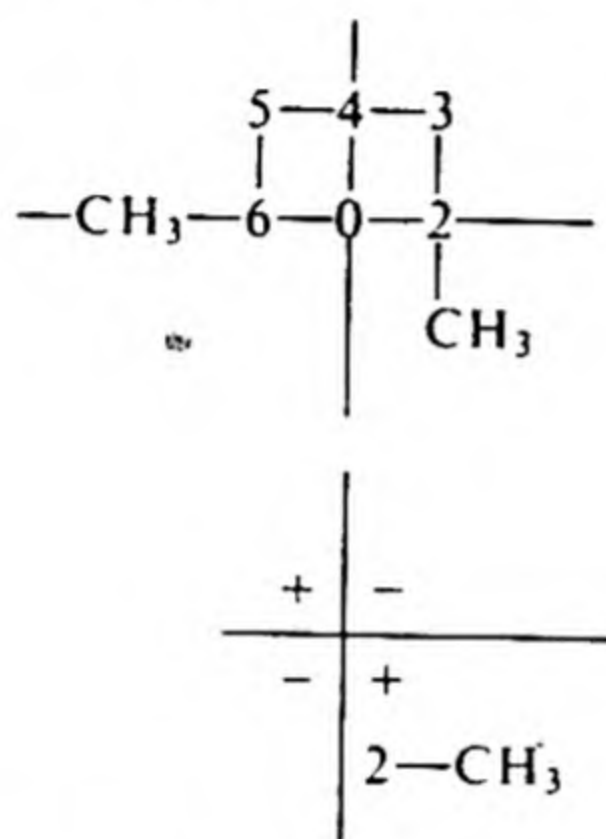
Answer



557 11

$$\begin{aligned}
 &x \times (\text{CH}_4 + 2\text{O}_2 \rightarrow \text{CO}_2 + 2\text{H}_2\text{O}) \\
 &y \times (\text{C}_2\text{H}_4 + 3\text{O}_2 \rightarrow 2\text{CO}_2 + 2\text{H}_2\text{O}) \\
 &z \times (2\text{CO} + \text{O}_2 \rightarrow 2\text{CO}_2) \\
 &x + y + 2z = 21.52 \text{ ml.} \\
 &x + 2y + 2z = 67.13 \text{ ml.} - 36.17 \text{ ml.} = 30.96 \text{ ml.} \\
 &2x + 3y + z = 78.38 \text{ ml.} - 36.17 \text{ ml.} = 42.21 \text{ ml.} \\
 &x + y + 2z = 21.52 \text{ ml.} \\
 &x + 2y + 2z = 30.96 \text{ ml.} \\
 &\quad y = 9.44 \text{ ml.} \\
 &x + 2z = 21.52 \text{ ml.} - 9.44 \text{ ml.} = 12.08 \text{ ml.} \\
 &4x + 2z = 84.42 \text{ ml.} - 56.64 \text{ ml.} = 27.78 \text{ ml.} \\
 &\quad 3x = 15.70 \text{ ml.} \\
 &\quad x = 7.85 \text{ ml.} \\
 &2z = 12.08 \text{ ml.} - 7.85 \text{ ml.} = 4.23 \text{ ml.} \\
 &\text{Vol. \% CH}_4 = \frac{100x}{21.52 \text{ ml.}} = \frac{100 \times 7.85 \text{ ml.}}{21.52 \text{ ml.}} = 36.4 \\
 &\text{Vol. \% CH}_2=\text{CH}_2 = \frac{100y}{21.52 \text{ ml.}} = \frac{100 \times 9.44 \text{ ml.}}{21.52 \text{ ml.}} = 43.9 \\
 &\text{Vol. \% CO} = \frac{100 \times 2z}{21.52 \text{ ml.}} = \frac{100 \times 4.23 \text{ ml.}}{21.52 \text{ ml.}} = 19.7
 \end{aligned}$$

Page Number	Question Number	Answer
638	1	Refractive dispersion is the variation in degree of <i>bending</i> of light at the interface between two media as the wavelength of light is varied. ORD is the variation in degree of <i>rotation</i> of plane polarized light within an optically active medium as the wavelength of light is varied. Measurement of ORD may depend on selection of wavelengths of light by means of a prism which produces refractive dispersion. (However, a diffraction grating may be used instead.)

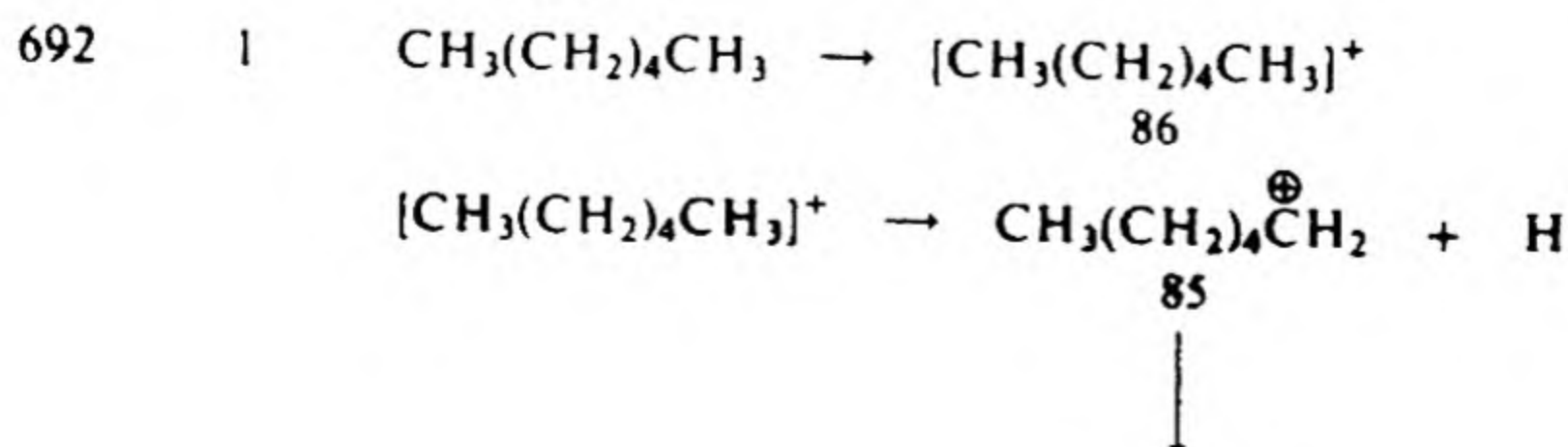


Predicted sign of Cotton effect is positive for the enantiomorph given.

- 675 5a There will be a single strong peak for 3 H at 6.7 τ and a single broader peak for 1 H at a position which depends on the concentration of the methanol in solution if the sample has moisture or a trace of acid. If the sample is pure, dry and acid-free, the OH peak will be a quartet and the CH₃ peak a doublet.

- 675 5c At ambient temperature, liquid ethane under pressure will have a single peak, a quartet at 9.1 τ . Both methyl groups are identical, and each interacts with the other in the same way. The *J* value will be about 4.5 cps.

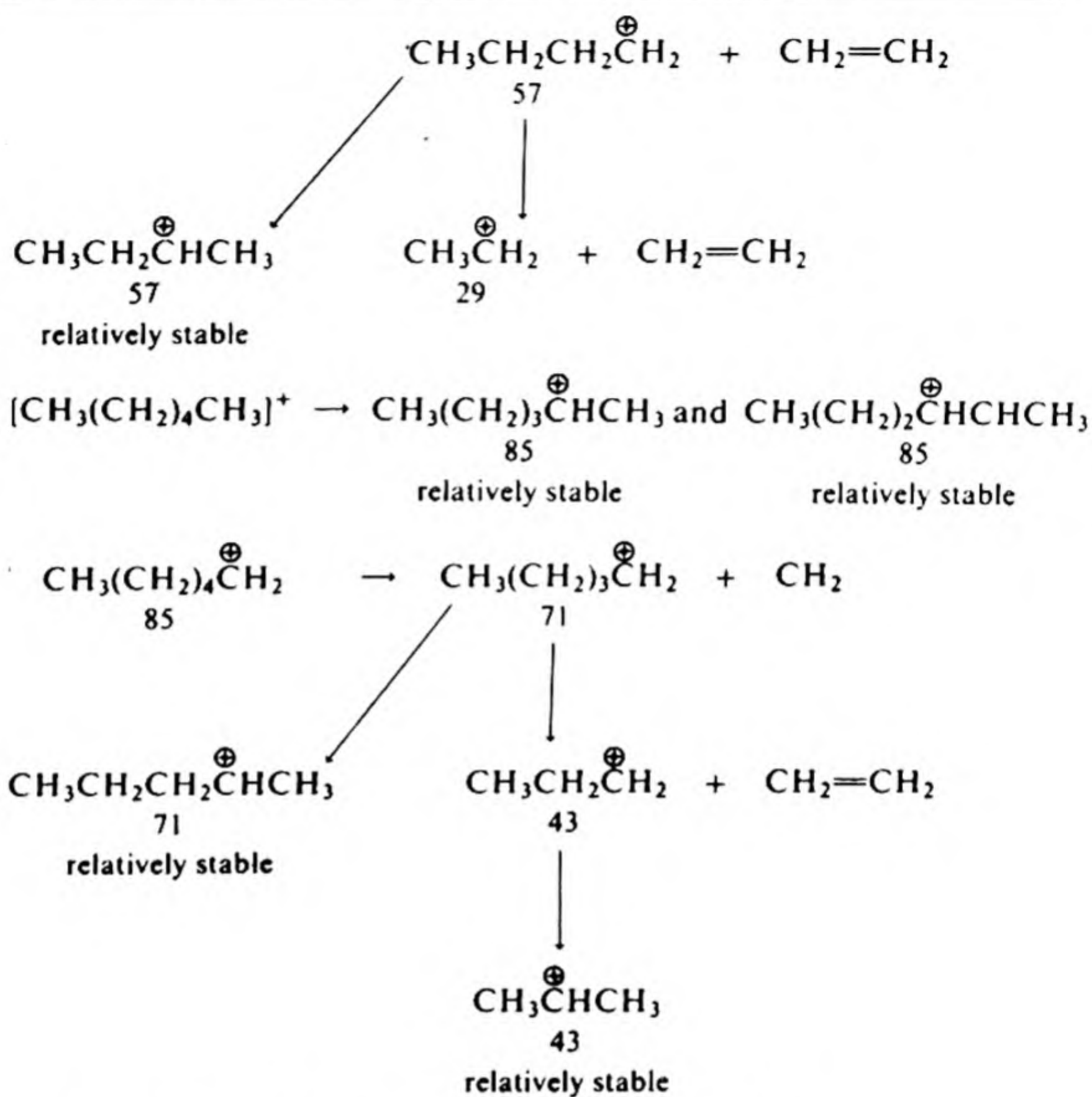
Liquid ethane just above its melting point would presumably show a more complex pattern because of "freezing" of the molecule in the staggered conformation, in which the effects of the different dihedral angles on *J* values in spin-spin splitting would show to a degree dependent on how much the rotations of the molecule were restricted.



Page Question
Number Number

Answer

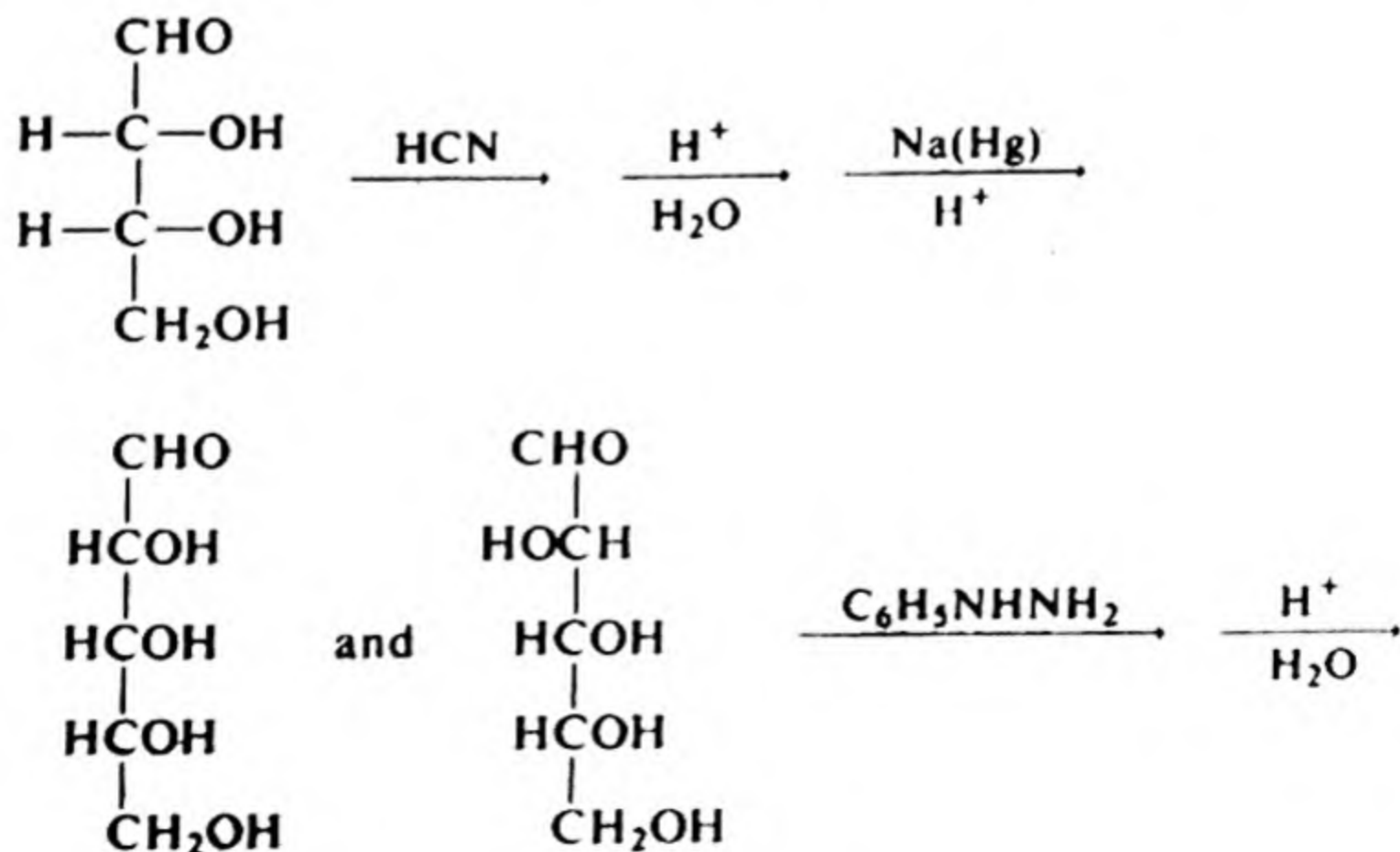
692 1
(continued)



Similar outlines can be written for 2,2-dimethylbutane.

728

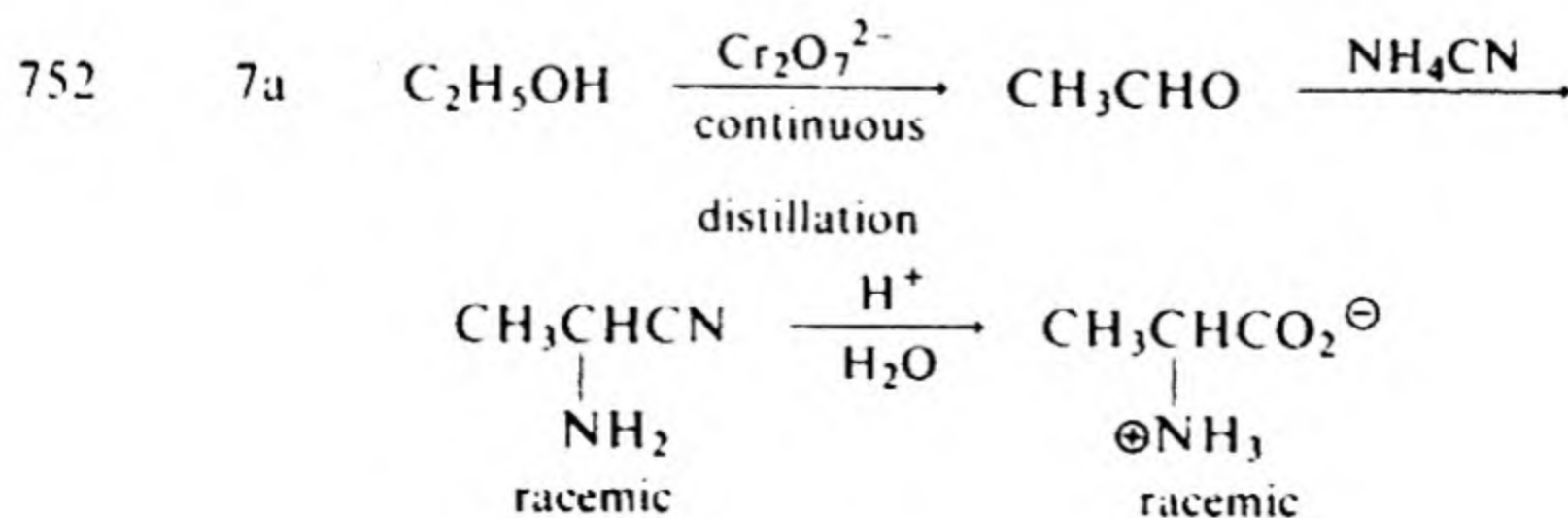
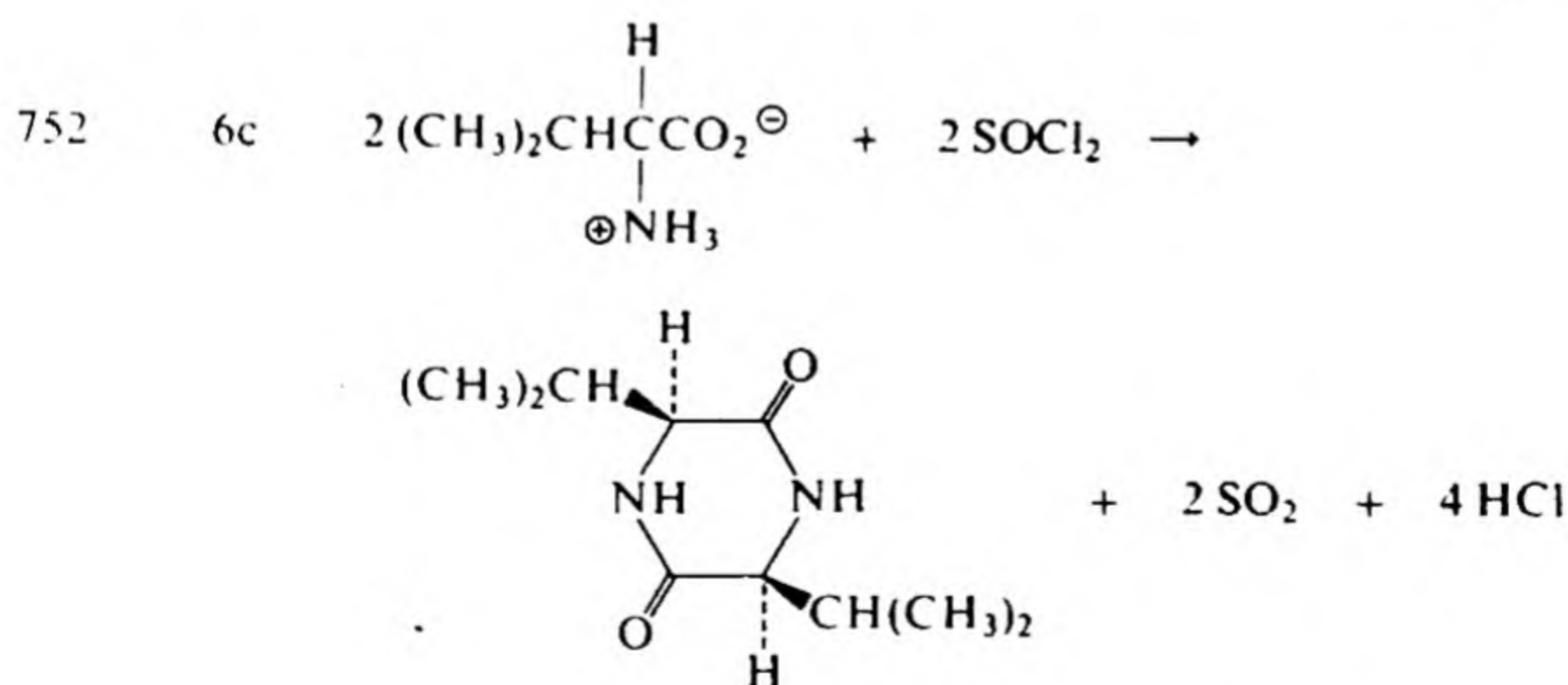
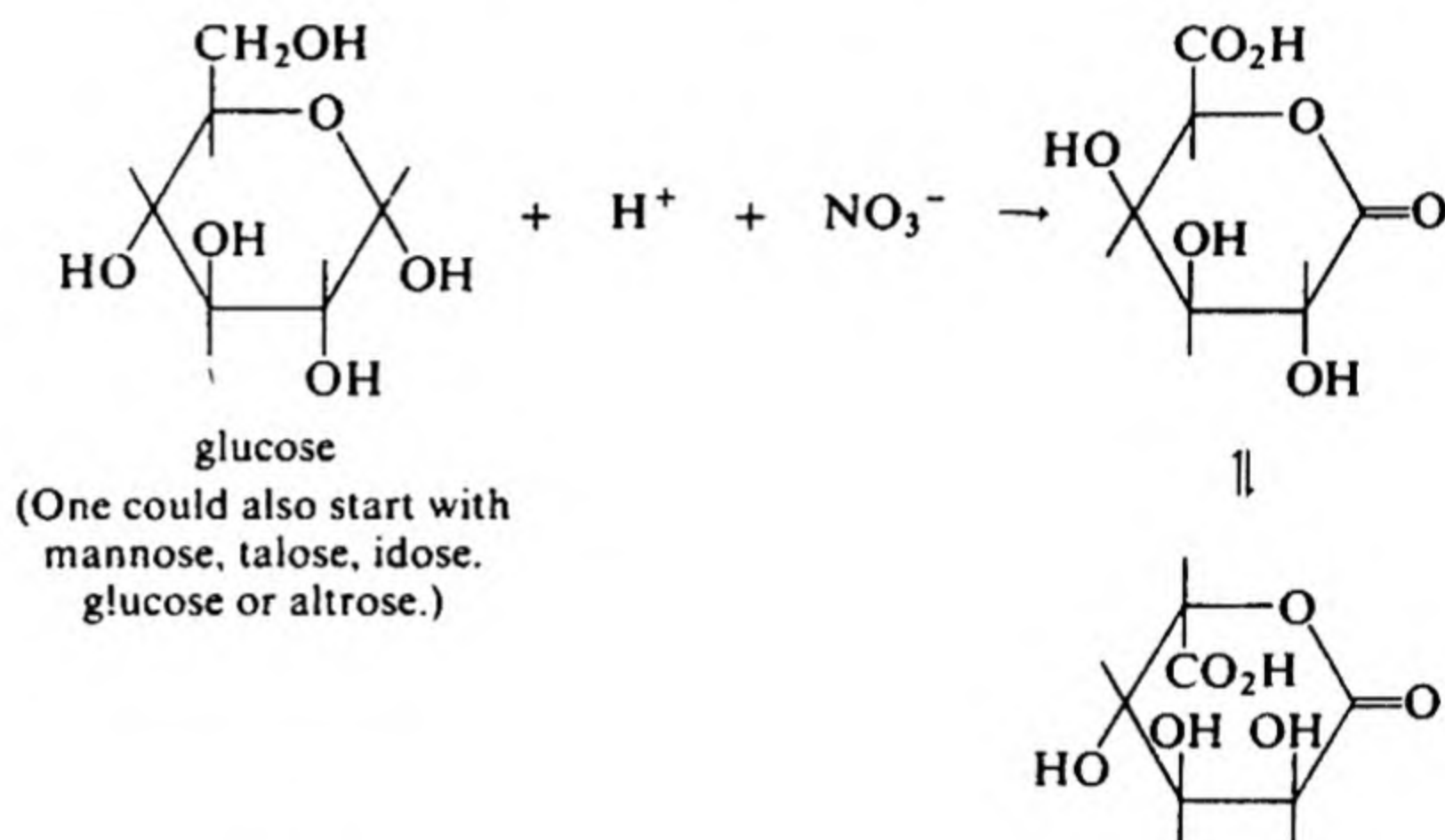
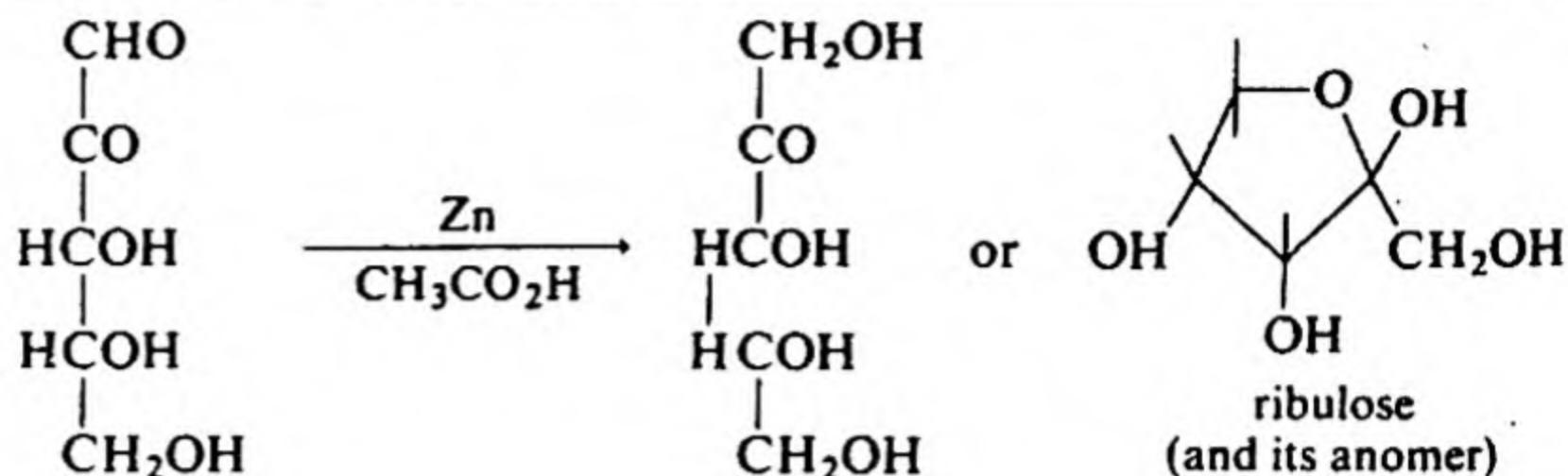
7a



Page Number Question Number

Answer

728 7a
(continued)



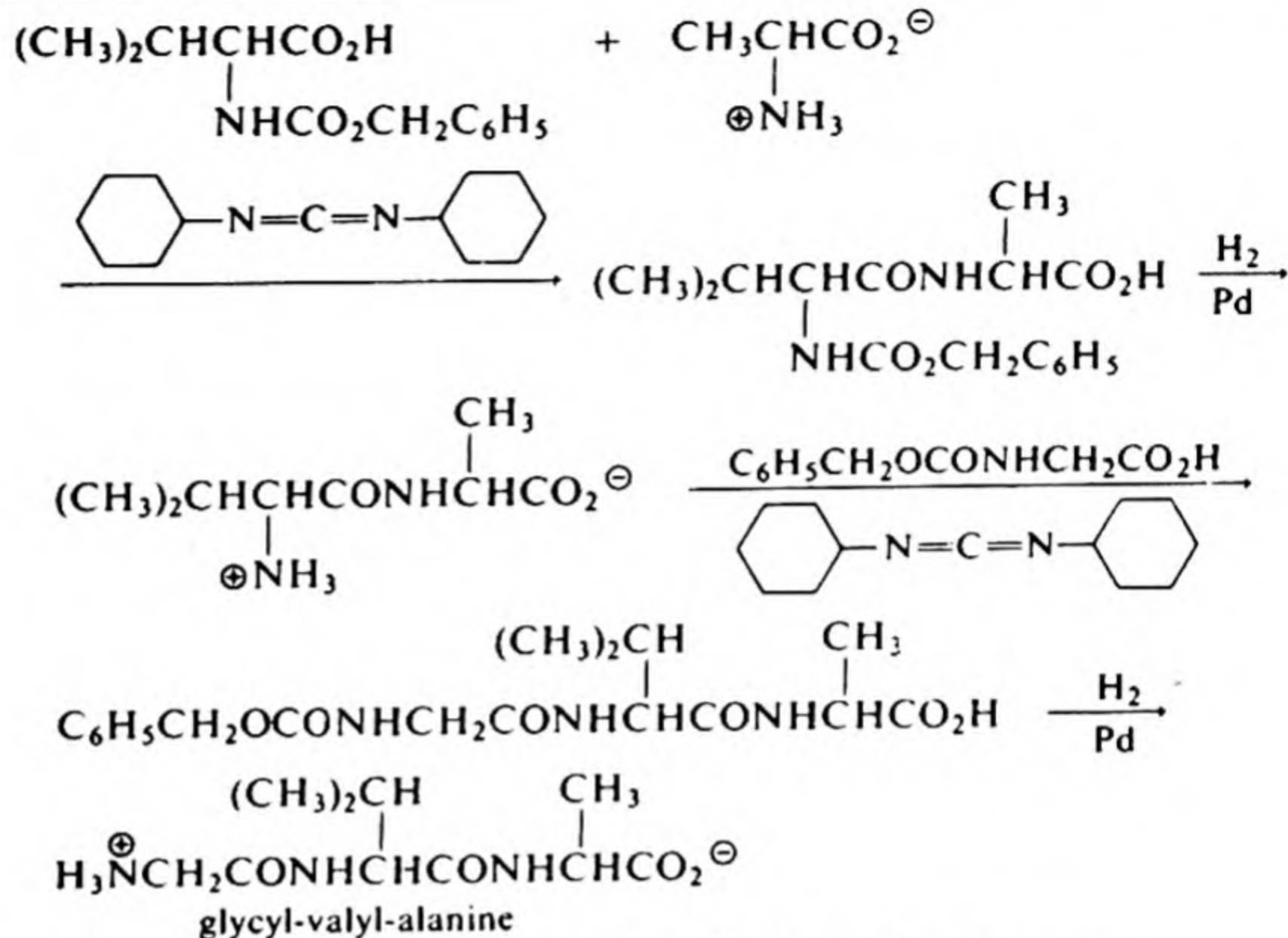
Page
Number

Question
Number

Answer

752

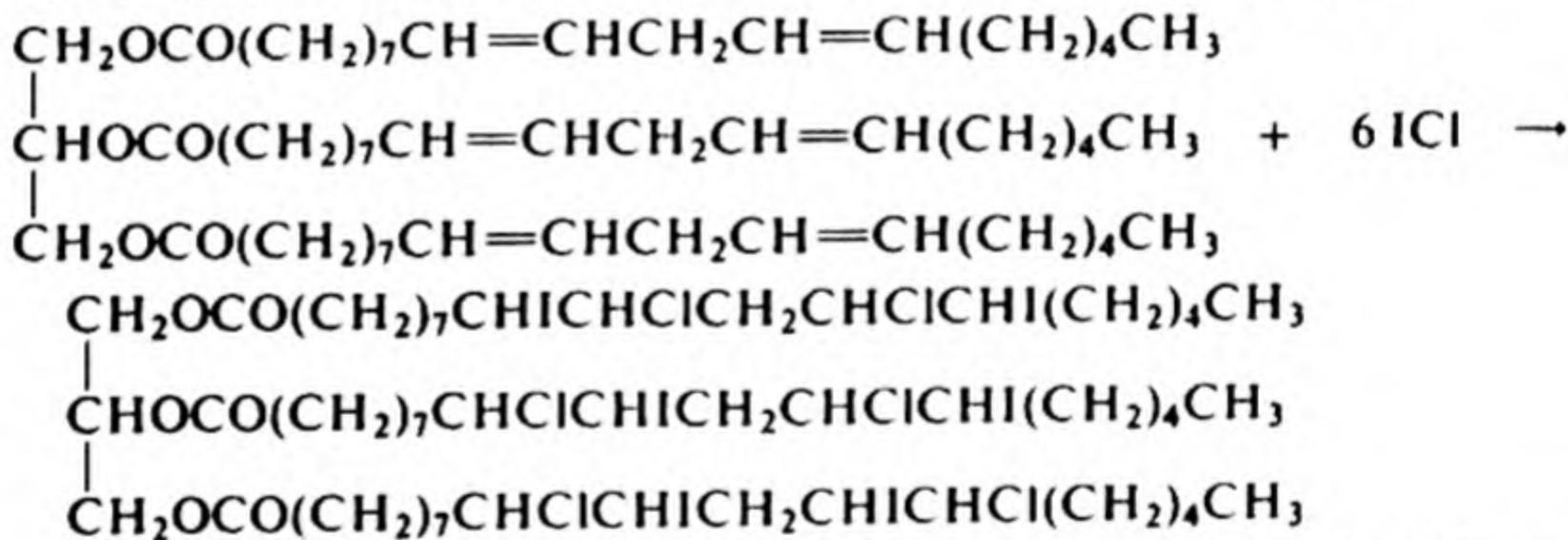
7b



The Fischer method or Woodward method may also be used.

768

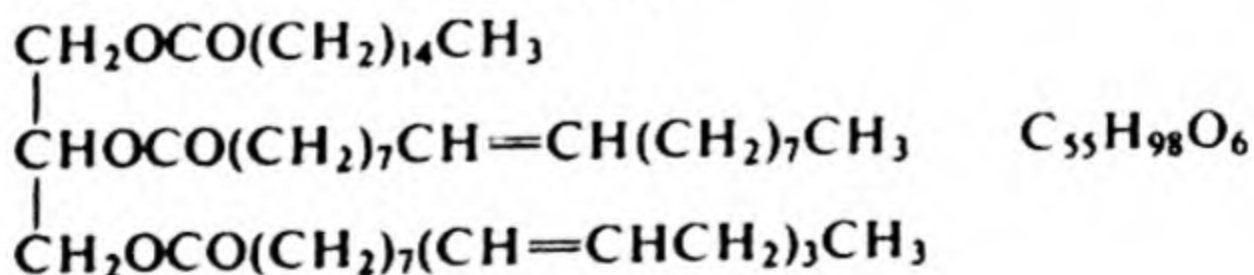
2d



The direction of addition of ICl is more or less random, as only very weak directive effects, if any, are present and Markovnikoff's rule is inoperative. (However, one iodine atom and one chlorine atom add at each double bond.)

768

3b



Molar wt. = 855.383 g.

Moles of iodine equivalent per mole of fat = 4

4 moles of I_2 = 1015.232 g.

$$\frac{1015 \text{ g. I}_2}{855.4 \text{ g. fat}} = \frac{x \text{ g. I}_2}{100 \text{ g. fat}}$$

$$x = 118.7 \text{ g. I}_2/100 \text{ g. fat} = \text{I}_2 \text{ no.}$$

Page Number	Question Number	Answer
768	5a	Bromine in CCl_4 reacts rapidly (decolorization observable) with the unsaturated fat in large amounts, whereas only a very small amount of bromine is decolorized by an essentially saturated fat. (No natural fats are known that are completely saturated.)
768	5c	Beeswax leaves an insoluble fatty alcohol residue upon saponification, whereas beef tallow dissolves completely in aqueous alkali upon saponification.
814	2h	
814	4a	$\text{CH}_3\text{CH}=\text{CHCH}_3 \xrightarrow[\text{or MnO}_4^-]{\text{OsO}_4, \text{H}_2\text{O}} \text{CH}_3\text{CHOHCHOHCH}_3$ <p style="text-align: center;"><i>cis</i> <i>meso</i></p> <p style="text-align: center;"> $\downarrow \text{O}_3$ $\downarrow \text{H}_2 \text{ Ni, H}_2\text{O}$ </p> <p style="text-align: center;"> $\text{CH}_3\text{CHO} \xrightarrow{\text{CH}_3\text{CHOHCHOHCH}_3} \xrightarrow{\text{H}^+} \text{CH}_3\text{C}(\text{CH}_3)_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_3$ </p> <p style="text-align: center;"> $\xrightarrow[\Delta]{\text{Pt}}$ </p> <p style="text-align: center;"> </p>
814	4e	$\text{CH}_2-\text{CH}_2 \xrightarrow{\text{Br}_2} \text{Br}(\text{CH}_2)_3\text{Br} \xrightarrow[\Delta, \text{NaHCO}_3]{(\text{H}_2\text{N})_2\text{CO}} \text{CH}_2\text{N}(\text{CH}_2)_3\text{C}(\text{O})\text{N}$
814	4h	$\text{CH}_3\text{CH}(\text{OC}_2\text{H}_5)_2 \xrightarrow{\text{H}^+} \text{CH}_3\text{CHO} \xrightarrow{\text{HCN}} \text{CH}_3\text{CHOHCN}$ $\text{CH}_3\text{CHOHCN} \xrightarrow[\text{HCl}]{\text{SnCl}_2} \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{CHOHCHO} \xrightarrow{\text{HBr}} \text{CH}_3\text{CHBrCHO}$ $\text{CH}_3\text{CHBrCHO} \xrightarrow{\text{H}_2\text{NNH}_2} \text{CH}_3\text{CH}=\text{CH}-\text{NH}-\text{N}=\text{CH}_2$

Page Number	Question Number	Answer
832	3d	$ \begin{array}{c} (\text{CH}_3\text{O})_2\text{PS}-\text{SCHCH}_2\text{CO}_2\text{C}_2\text{H}_5 \\ \\ \text{CO}_2\text{C}_2\text{H}_5 \\ \uparrow \\ \text{light} \\ (\text{CH}_3\text{O})_2\text{PSSH} \quad + \quad \begin{array}{c} \text{CHCO}_2\text{C}_2\text{H}_5 \\ \\ \text{CHCO}_2\text{C}_2\text{H}_5 \end{array} \\ \uparrow \text{P}_2\text{S}_5 \qquad \qquad \qquad \uparrow \text{H}^+ \text{C}_2\text{H}_5\text{OH} \\ (\text{CH}_3\text{O})_2\text{POSH} \qquad \qquad \qquad \begin{array}{c} \text{CO} \\ \diagup \quad \diagdown \\ \text{CH} \quad \text{O} \\ \quad / \quad \backslash \\ \text{CH} \quad \text{CO} \end{array} \\ \uparrow \text{H}_2\text{S} \\ (\text{CH}_3\text{O})_2\text{POCl} \\ \uparrow \text{POCl}_3 \\ \text{CH}_3\text{OH} \qquad \qquad \qquad \begin{array}{c} \text{O}_2 \uparrow \text{V}_2\text{O}_5 \\ \text{C}_6\text{H}_6 \end{array} \end{array} $
833	6	Biotin
840	2a	<i>n</i> -Pentane The longer a continuous chain, the lower the octane number.
840	2c	2,3,3-Trimethylpentane Centrally substituted hydrocarbons have higher octane numbers than terminally branched ones.
840	2e	Methylcyclohexane Cycloalkanes have higher octane numbers than isomeric alkanes of equivalent branching.
849	2a	$\text{Si}-\text{Si} > \text{C}-\text{Si} > \text{C}-\text{C}$ toward acidic or basic reagents $\text{Si}-\text{Si} > \text{C}-\text{C} > \text{C}-\text{Si}$ toward thermal decomposition
849	2c	$\text{Si}-\text{Cl} > \text{C}-\text{Cl}$
849	2e	$\text{C}-\text{Cl} > \text{C}-\text{F} > \text{C}-\text{H}$ toward nucleophiles and active metals $\text{C}-\text{H} > \text{C}-\text{Cl} > \text{C}-\text{F}$ toward oxidation $\text{C}-\text{Cl} > \text{C}-\text{H} > \text{C}-\text{F}$ toward thermal decomposition
849	3a	$ \begin{array}{c} \text{CH}_2=\text{CH}_2 \xrightarrow{\text{HBr}} \text{C}_2\text{H}_5\text{Br} \xrightarrow[\text{dry ether}]{\text{Mg}} \\ \text{C}_2\text{H}_5\text{MgBr} \xrightarrow{\text{SiCl}_4} (\text{C}_2\text{H}_5)_3\text{SiCl} \xrightarrow{\text{H}_2\text{O}} \\ (\text{C}_2\text{H}_5)_3\text{SiOSi}(\text{C}_2\text{H}_5)_3 \end{array} $

Page Number	Question Number	Answer
870	4a	$\text{C}_2\text{H}_2 \xrightarrow{\text{Cu}^+} \text{CH}_2=\text{CHC}\equiv\text{CH} \xrightarrow[\text{pressure}]{\text{HCl}}$ $\text{CH}_2=\text{CHC}(\text{Cl})=\text{CH}_2$
870	4d	$\text{C}_6\text{H}_6 \xrightarrow[\text{H}_2\text{SO}_4]{\text{HNO}_3} \xrightarrow[\text{HCl}]{\text{Fe}} \text{C}_6\text{H}_5\text{NH}_2 \xrightarrow{\text{CH}_2\text{O}}$ $\text{C}_6\text{H}_5\text{NH}-\text{CH}_2-\text{NH}-\text{C}_6\text{H}_5 \xrightarrow[\Delta]{\text{H}^+}$ $\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{CH}_2-\text{C}_6\text{H}_4-\text{NH}_2$
870	5	$\text{C}_6\text{H}_5\text{OH} \xrightarrow[\text{pressure}]{\text{H}_2, \text{Ni}} \text{C}_6\text{H}_{11}\text{OH} \xrightarrow[\text{H}^+]{\text{Cr}_2\text{O}_7^{2-}}$ $\text{HOCO}(\text{CH}_2)_4\text{CO}_2\text{H} \xrightarrow[\Delta]{\text{NH}_3} \text{NC}(\text{CH}_2)_4\text{CN} \xrightarrow[\text{Ni}]{\text{H}_2}$ <p style="text-align: center;">adipic acid</p> <p style="text-align: center;">$\text{H}_2\text{N}(\text{CH}_2)_6\text{NH}_2$ hexamethylenediamine</p>

Index

- ADP, 750
- AMP, 750
- ATP, 750
- Abbe refractometer, 604-605
- Abietic acid, 776
- Abnormal bimolecular displacement reaction, 275
- Absorption curves
 - band spectrum and, 642
 - for benzene, 643
- Absorption of light, 633
 - color and, 650
 - law of, 643-644
 - spectra and, 639
 - by vibrational transition, 642
 - wavelength, 649
- Absorption maxima, 643
- Absorption minima, 643
- Absorption peaks, 643
- Absorption spectrum, 639
- Acetal, 400
 - formation of, 398-401
 - phospholipids, 766-767
- Acetaldehyde, 150, 170-172, 324, 453, 490
- Acetamide, 252
- Acetanilide, 354
- Acetate ion, 252
- Acetates, 304
- Acetic acid, 3, 92, 149, 166, 210, 252
- Acetic anhydride, 556
- Acetoacetic esters
 - dialkylated, 466
 - monoalkylated, 466
 - syntheses
 - of acids, 466-467
 - of ketones, 466-467
- Acetoacetyl, 779
- β -Acetonaphthalene, 530
- Acetone, 91, 185
- Acetyl chloride, 166
- Acetyl coenzyme A, 751
- Acetylenes, 35, 66
 - additions to, 326-327, 477-478
 - reaction with, 397-398
- Acetylenic bonds, 129-130
- Acid-catalyzed reaction, 254
- Acid chlorides, 379-380
- Acid derivatives
 - additions in, 371-391
 - displacements in, 371-391
 - Grignard reagents and, 439-440
 - solvolysis of, 376-387
- Acid dyes, 654, 655
- Acidity, 118
 - in carboxylic acids, 148-153
 - in miscellaneous groups, 217
 - molecular factors producing and modifying, 207-209
 - and organic acids, 207-218
 - in organic compounds, 205-223
 - in phenols, 148-153
 - of proteins, 739-740
- Acids
 - abietic, 776
 - acetoacetic ester syntheses of, 466-467
 - cis*-aconitic, 724
 - adipic, 381, 866
 - agathic, 776
 - aldonic, 698
 - amino, 731-736
 - chemical properties of, 733-736
 - naturally occurring, 732-736
 - physical properties of, 733
 - sources, 731
 - p*-aminobenzoic, 733, 818, 830
 - α -aminocarboxylic, 731
 - aniline bisulfate, 526
 - anisic, 215
 - arachidonic, 756
 - Arrhenius theory, 205
 - arsanilic, 421
 - L-ascorbic, 710, 819
 - L-aspartic, 733
 - atrolactic, 629
 - barbituric, 804
 - benzenecarbohydroxamic, 382
 - benzilic rearrangement, 521-522
 - benzoic, 213, 214, 215, 384, 556

Acids (*continued*)

- Brønsted, 794
- Brønsted-Lowry theory, 205-206
- sec*-Butyl bromide, 288
- butyric, 209-210
- carboxylic, 82, 514
 - malonic ester syntheses of, 463-466
- chloroacetic, 209
- chlorosuccinic, 630
- cholic, 780
- cinnamic, 459, 547
- citric, 724
- conjugate, 283
- cyclopentanecarboxylic, 523
- definition of, 205-207
- dehydroascorbic, 819
- deoxyribonucleic, 812-813
- dichloroacetic, 209
- 2, 4-dichlorophenoxyacetic, 824
- 1, 3-diphosphoglyceric, 723
- 2-dodecenedioic, 822
- durenesulfonic, 524
- enolpyruvic, 723
- fatty
 - biogenesis of, 759-760
 - degradation of, 759-760
 - reduction of, 578-579
- folic, 816
- folinic, 751
- formic, 83, 84
- fumaric, 250, 724
- galacturonic, 721
- glucaric, 698
- gluconic, 698
- glucuronic, 698
- L-glutamic, 733
- glycaric, 698
- glycocholic, 781
- glycuronic, 698
- guanylic, 812
- halogen, 284
- heptanoic, 699
- hippuric, 381
- hydrolipoic, 726
- hydroxamic, 382-383
- indole-3-acetic, 822
- γ -indole-3-butyric, 824
- L-iodogorgoic, 732
- isocitric, 724
- α -ketoglutaric, 724
- levulinic, 859
- Lewis theory, 207
- linoleic, 756
- linolenic, 756
- lipoic, 726
- maleic, 250
- malic, 630, 724
- mandelic, 629
- meta*-substituted, 214-216
- methacrylic, 406
- 1-methylglucuronic, 561
- β -naphthalenacetic, 530
- naphthalene-1-acetic, 824
- α -naphthalenesulfonic, 524
- nicotinic, 816
- nitric, 117
- m*-nitrobenzoic, 504
- m*-nitrophenylacetic, 504
- nitrous, 500-501
- nucleic, 810, 812-813
- oleanolic, 777
- oleic, 756
- ortho*-substituted, 216
- oxalylacetic, 724
- oxalylsuccinic, 724
- pantothenic, 830
- para*-substituted, 214-216
- peracetic, 592
- perbenzoic, 556
- phenylacetic, 213
- γ -phenylbutyric, 582
- β -phenylpropionic, 530
- phenylpyruvic, 578
- N*-phenylsulfamic, 526
- 2-phosphoenolpyruvic, 723
- 2-phosphoglyceric, 723
- 3-phosphoglyceric, 723, 726
- picric, 212
- pimaric, 776
- prehnitenesulfonic, 524
- pteroylglutamic, 816
- pyruvic, 723, 724
- ribonucleic, 812
- saccharic, 698
- sebacic, 381
- solvolysis of, 376-387
- stearic, 756
- strength increased, 208
- succinic, 724
- sulfanilic, 526
- sulfinic, 566
- sulfonic, 85
- sulfuric, 83, 84, 117
- tannic, 711
- 2 (R), 3 (R)-tartaric, 625
- taurocholic, 781
- traumatic, 822
- trimethoxyglutaric, 703
- uric, 811
- cis*-Aconitic acid, 724
- Acridine yellow G, 656
- Acridines, 656, 789

- Acrolein, 321
 Acrylonitrile, 323, 477
 additions to, 474
 Activation energy, 232
 Active hydrogen, *see* Hydrogen, active
 Acyl chloride, 84
 enol of, 450
 Acyl halide, 84
 Acyl nitrosoamines, 495
 Acylation, 345-347
 Acylnitrene, 515
 Addition reactions, typical, 321-325
 Adenine, 811, 813
 Adenosine, 812
 Adenosine triphosphate, 750
 Adipic acid, 381, 866
 Adiponitrile, 577
 Adrenaline, 821
 Agar agar, 721
 Agars, 721
 Agathic acid, 776
 Aglycone, 711
 Air, oxidation by, 550-557
 β -Alanine, 733
 L-Alanine, 732
 Albuminoids, 737
 Albumins, 737
 Alcohols, 80-81, 579
 n-amyl, 428
 coniferyl, 727
 dehydrations of, 298-299
 diacetone, 457
 dodecyl, 583
 endo, 594
 ethyl, 454
 exo, 594
 isobutyl, 428
 NMR spectra of, 672
 neopentyl, 489
 oxidation of, 556, 560-561
 pentaerythritol, 489
 polyvinyl, 863
 tert-amyl, 511
 tert-butyl, 384
 tertiary, 388
 Aldehyde ammonias, 417-418
 Aldehydes, 82, 156, 453
 addition products of, 396-407
 decarbonylation of, 543
 enol of, 450
 Grignard reagents and, 437-438
 oxidation of, 556, 561-562
 reactions of, 392-419
 unsaturated, 474-476
 Aldehydic oxygen, 132
 Alder, Kurt, 588
 Aldol condensations, 457-458
 Aldonic acid, 698
 Aldoses, 700-701
 configurations of, 706-709
 degradation of, 699
 Aldrin, 592
 Alicyclic, 77
 Aliphatic alcohols, 284
 Aliphatic amines, 217, 500-501
 Alizarin yellow R, 654
 Alizarins, 657
 Alkaline hydrolysis, 241
 Alkaloids, 802-803
 Alkanedioic acids, 182-183
 Alkanes, 60, 121, 179
 branches, 93-94
 higher, 93
 normal, 92
 Alkatienes, 252
 Alkene oxide, 307-
 Alkenes, 65-66
 oxidation of, 557-559
 Alkoxide ion, 135, 210, 211
 Alkoxy group, 283, 285
 Alkoxyl oxygen, 221
 Alkyd resins, 866
 Alkyl acid sulfates, 217-218, 286
 Alkyl aryl ethers, 285
 Alkyl bromides, 139, 239
 Alkyl cellosolve, 791
 Alkyl chlorosilanes, 842
 Alkyl ethyl ether, 267
 Alkyl group, 60-61
 Alkyl halides, 78, 123, 126-127, 179, 261, 275, 283
 dehydrohalogenations of, 292-293
 formation with inorganic halides, 289-290
 Alkyl hydroperoxides, 519-520
 Alkyl iminoethyl ethers, 252
 Alkyl nitrite, 169, 267
 Alkyl-oxygen bonds, 155
 Alkyl sulfates, 286
 Alkyl sulfonates, 276
 Alkylamines, 123, 153
 Alkylarenesulfonates, 765
 Alkylation, 838-839
 reactions, 344-345, 504-505
 reductive, 577-578
 Alkylchlorosilanes, 842
 Alkylcyclohexenes, 299
N-Alkyldithiocarbamates, 413
 Alkyloxonium ions, 283
 Alkyloxy group, 133
 Alkylpentazole, 806
 Alkylphthalimides, 278
 Alkynes, 66

- Allantoin, 811
 Allene, 67
 enantiomorphous, 621
 Allethrin, 825
 D-Allose, 707
 Alloxazine, 790
 Allyl bromide, 322
 Allyl cation, 252, 272, 320
 Allyl chloride, 271, 332
 Allyl halides, 252
 Allyl isopropenyl ether, 529
 Allylacetone, 529
 Allylic rearrangements, 273-275
 D-Altrose, 707
 Alumina, 284, 299
 Aluminohydrides, 53
 Aluminum chloride, 118, 218
 Ambident ions, 280
 Ambiprotic substances, 206
 Amide-formaldehyde polymers, 867-868
 Amides, 86-87, 500-501
 basicity in, 152-154
 dimeric, 181
 hydrolysis and, 380-383
 orbital formula for, 154
 Amidines, 222
 Amido yellow E, 656
 Amine-formaldehyde polymers, 867-868
 Amine-oxide decompositions, 304
 Amines, 86, 123, 296
 aliphatic, 500-501
 Hofmann synthesis of, 278
 tertiary, 126
 Amino acids, 731-736
 chemical properties, 733-736
 naturally occurring, 732-733
 physical properties of, 733
 sources, 731
p-Aminoazobenzene, 526, 527
p-Aminobenzoic acid, 733, 818, 830
p-Aminophenol, 526
 2-Aminopyridine, 802
 Ammonia, 13, 86, 153
 aldehyde, 417-418
 Ammonium compounds, 261
 Ammonium salts, 126
 Ammonium sulfide, 585-586
 Amphoteric compounds, 153, 206
 Amygdalin, 711
n-Amyl alcohol, 428
tert-Amyl alcohol, 189, 319, 511
tert-Amyl bromide, 288
tert-Amyl cation, 512
 Amylopectin, 719
 Amylose, 719
 Amytal, 805
 Analogous reaction, 207
 Analogs
 oxygen, 85
 sulfur, 85
 thio, 85
 Anchimeric assistance, 306
 5- β -Androstane, 780
 5- α -Androstane, 780
 Androstenediol, 782
 Δ^1 -Androstenedione, 782
 Angular momentum constant, 21
 Anhydride, 84
 acetic, 556
 maleic, 555, 588
 phthalic, 555
 reactions of, 379-380
 with active hydrogen, 455
 Aniline, 91, 194, 583
 absorption spectra of, 652
 n-substituted, 526-528
 Aniline bisulfate, 526
 Anionic species, 314
 Anisate ion, 216
 Anisic acid, 215, 252
 Anisole, free energy diagrams for, 358
 Anthocyanins, 798
 Anthracene, 76, 145, 336, 485, 584, 589
 Antibiotics, 831
 Antibodies, 828
 Antibonding orbital, 31
 Antidiazosulfonates, 660
 Antiseptics, 828-829
 Antitoxins, 828
 Apoenzymes, 748
 D-Arabinose
 Arachidonic acid, 756
 Arene-antidiazosulfonate, 660
 Arenediazoamino compound, 660
 Arenediazonium salts, 495
 Arenes, 77
 resonance energies of, 147
 Arene sulfonate salts, 486
 L-Arginine, 732
 Argon pattern, 23
 Arndt-Eistert synthesis, 504, 514
 Aromatic compounds
 correlation of structure with reactivity in,
 339-340
 oxidation of, 555-556, 559-560
 relative reactivities of, 354
 Aromatic nucleophilic displacements
 478-481
 via aryne intermediates, 482-486
 Aromatic rearrangements, 523-529
 Aromatic ring, 154, 271
 Aromatic ring condensations, 460-463

- Aromatic sigma complex, 339
 Aromatic systems, 76
 Aromaticity, 109-110, 140-148
 Arrhenius, Svante, 205, 239
 Arsanilic acid, 421
 Aryl, 209
 Aryl cations, 290
 Aryl chlorides, 423
 1-Aryl-3,3-difluoro-2,2-dichloro-cyclobutene, 596
 Aryl halides, 126-127, 155
 Aryl-halogen bonds, 155
 Arylamines, 219
 basicity in, 152-154
 Arylammonium ions, 154, 219
 Arylmagnesium, 422-423
 Aryloxide ions, 151
 Arynes, 243, 482-486
 aromatic nucleophilic displacements via, 482-486
 Ascaridole, 546
 L-Ascorbic acid, 710, 819
 L-Asparagine, 732
 L-Aspartic acid, 733
 Associated form, 181
 Asymmetric atoms, 620
 Asymmetric carbon atoms, 614, 619-620
 Asymmetric molecules, 620-622
 Atabrin, 797
 Atactic polymers, 854
 Atomic dimensions, 37
 Atomic nuclei, magnetic properties of, 669
 Atomic orbitals, 28-30, 140, 142
 sublevels and their relative energies, 24
 Atomic particles, spin properties of, 667-668
 Atomic refractions, 607
 Atomic structure, 20-24
 Atrolactic acid, 629
 Aufbau principle, 22, 30
 Autoclave, 253
 Autoxidation, 541, 556
 reactions, 540-541
 Auxin A, 822
 Auxin B, 822
 Auxins, 822
 synthetic, 823-925
 Auxochromes, 650-652
 Avertin, 492
 Avogadro's law, 6
 1-Azanaphthalene, 789
 2-Azanaphthalene, 789
 10-Azanthracene, 789
 Axial groups, 73
 Azeotropic distillation, 286
 Azimuthal quantum number, 21
 1-Azindene, 789
 2-Azindene, 789
 Azine dyes, 656
 Aziridene, 787
 Azo compounds, 498
 Azo coupling reactions, 347-348
 Azobenzene, 583
 Azoisobutyronitrile, 336, 851
 Azolidine, 787
 Δ^2 -Azoline, 787
 Δ^3 -Azoline, 787
 Azonium ion, 516
 Azoxybenzene, 583

 BAL, 829
 Baeyer, Adolph von, 71, 118, 785
 Baeyer system of nomenclature, 595
 Baeyer test, 130, 557-558
 Baeyer-Villiger reaction, 520
 Barbitol, 805
 Barbiturates, 465, 804-805
 Barbituric acid, 804
 Base-promoted reactions, 254
 Bases
 Brønsted-Lowry theory, 205-206
 definition of, 205-207
 as inorganic reagent, 46
 Lewis theory, 207
 strength of various, 220
 strong organic, 222-223
 weak, in strong acid solutions, 221-222
 Basicity, 122
 in amides, 152-154
 in arylamines, 152-154
 and basic organic compounds, 218-223
 comparison in organic compounds, 219
 molecular factors producing and modifying, 218-219
 in organic compounds, 205-223
 of proteins, 739-740
 Bathochromic shift, 648
 Beauval-Banc reduction, 583
 Beckmann differential thermometer, 9
 Beckmann rearrangement, 516-519
 Beer-Lambert law, 643
 Benedict's reagent, 698
 Benzalacetone, 458
 Benzalacetophenone, 322, 475
 Benzaldehyde, 171, 276, 418, 490, 493, 556, 560
 Benzene, 76, 140-148, 154, 172, 425, 836
 absorption curves for, 643
 absorption spectra of, 652
 dipole moments of, 352
 free energy diagram for, 360, 356, 358
 proposed structures of, 142

- Benzene (*continued*)
 reactivity toward nitration, 354
 resonance energy diagram for, 143
 Benzene rings, 213, 214
 Benzenecarbohydroxamic acid, 382
N-Benzenediazoaniline, 526
 Benzenediazonium chloride, 495
 Benzenesulfonic acid, 217
 Benzhydrazide, 382
 Benzidine, 527
 Benzilic acid rearrangement, 521-522
 Benzoate ion, 213
 Benzoates, 304
 Benzo [b] pyrazine, 790
 Benzo [b] pyridine, 790
 1-Benzo [b] pyrrole, 789
 Benzo [b] thiophene, 789
 Benzo [c] pyridine, 789
 2-Benzo [c] pyrrole, 789
 Benzo [d] pyrimidine, 789
 Benzofuran, 791
 Benzohydril ion, 272
 Benzoic acid, 213, 214, 215, 384, 556
 reactivity toward nitration, 354
 Benzoin condensation, 492-493
 Benzophenone, 546
 Benzophenone hydrazone, 506
 Benzoquinone, 492
 Benzoyl chloride, 452
 Benzoyl peroxide, 329, 851
 Benzyl benzoate, 490
 Benzyl cation, 272
 Benzyl chloride, 271
 reactivity toward nitration, 354
 Benzyl free radicals, 535
 Benzyl penicillin, 831
 Benzylidene chloride, 276
 Benzylideneacetone, 458
 Benzyne, 484-485
 Beta eliminations, 292-303
 Bicarbonate ion, 151
 Bicyclohexyl, 75-76
 Bifluoride ion, 41
 Bimolecular, 231, 262
 Bimolecular attacks, 274
 Biodegradable, 764
 Biogenesis of fatty acids, 759-760
 Biotin, 167, 818, 830
 Biradicals, 52
 Birch reduction, 583
 Birefringence, 609
 in Iceland spar, 610
 separation of light into polarized beams
 by, 611
 Bisabolene, 774
 Bischler-Napieralski synthesis, 798
 Biuret reaction, 740
 Blankophor R, 659
 Blue
 Capri, 656
 emission and absorption relationships, 650
 indigo, 657
 methylene, 663
 Boiling point, 6-7, 179
 of continuous-chain aliphatic organic
 compounds, 180
 Boltzmann distribution, 232
 Bond angles, 31-32
 Bond distance, 26-27
 Bond energies, 238
 Bond hybridization, 32
 Bonding
 chemical, 20-53
 covalent, 25-27
 dissociation energies, 26-27
 hydrogen, 40-41
 Bonding orbital, 31
 Bonds
 acetylenic, 129-130
 alkyl-oxygen, 155
 aryl-halogen, 155
 carbon-bromine, 239, 241
 carbon-carbon, 117-118
 carbon-chlorine, 242
 carbon-halogen, 124-127
 carbon-heteroatom, 124, 127, 131-136, 155
 carbon-nitrogen, 124-127
 carbon-oxygen, 124-127
 hybridization, 119
 to hydrogen, 118-122
 multiple, 33-35, 65-68, 129-136
 carbon-heteroatom, 131-136
 olefinic, 129-130
 semi-ionic, 47
 single, 117-127
 Boord synthesis, 433
 Bornane, 506
 Bornene, 772
 Bornyl chloride, 773
 Borohydrides, 53
 Boron trifluoride, 207, 284
 Bragg equation, the, 685
 Bridgehead atoms, 76
 British anti-Lewisite, 829
 Bromide ion, 45
 Bromides, 179
 alkyl, 139
 ethylcadmium, 440
 vinyl, 139-140
 Bromine, 120, 129, 314-315
 Bromine atoms, 331
 Bromoacetophenone, 450

- Bromobenzene, 155
 reactivity toward nitration, 354
m-Bromochlorobenzene, 437
 (S)-Bromochlorofluoromethane, 625
 Bromocyclohexane, 120
 2-Bromofuran, 795
 Bromohydrin, 321
 Bromoketone, 450
 Bromonium ion, 315
 Bromopropionaldehyde, 321
 Bromopropionitrile, 323
 Bromostyrene, 294-295
 2-Bromothiophene, 795
 Bromotrichloromethane, 335
 Brønsted, J. N., 205
 Brønsted acid, 118, 794
 Brønsted base, 122, 218, 260
 Brønsted-Lowry theory, 205-206
 Buna rubber, 860
 Butadiene, 320, 860
 Butadiene molecule, 67-68
 Butadiene-styrene copolymer, 860
 Butane, 60
 mass spectra of, 691
 normal, 15-16
 molecular models of, 16
 Butene, 169
 Butoxide ion, 294
 Butyl alcohol, 210
tert-Butyl alcohol, 296, 384
tert-Butyl benzoate, 384
sec-Butyl bromide, 288
tert-Butyl bromide, 241, 243, 288
 Butyl chloride, 284
 Butyl halides, 295, 268
tert-Butyl hydroperoxide, 541
tert-Butyl methyl ether, 384
t-Butyl peroxide, 569
 Butyl rubber, 861
 Butylamine, 278
tert-Butylbenzene, 345, 354
 Butyldimethylammonio, 126
 Butyltrimethylammonium hydroxide, 303
 Butyric acids, 209-210

 Cadalene, 775
 Cadinene, 774
 Caffeine, 811
 Calciferol, 547
 Calorimeter, 237
 Calvin, Melvin, 725
 Camphene, 772, 773
 Camphene hydrochloride, 773
 Camphor, 772
 Camphor hydrazone, 506
 Cannizzaro reaction, 488-489

 Canonical structures, 144
 Capri blue, 656
 ω -Caprolactam, 866
 Captan, 827
 Carbanion processes, 297-298, 853
 Carbanions, 243
 Carbazole, 789
 Carbenes, 243, 308-312
 rearrangements, 514
 structures and reactivities of, 308-311
 Carbohydrates, 695-730
 classification of, 695
 disaccharides, 712-715
 glycosides, 711-712
 metabolism of, 722-725
 monosaccharides, 695-711
 polysaccharides, 715-722
 Carbon
 asymmetric atoms, 614, 619
 atomic structure of, 42
 migrations of, 511-521
 multiple bonds of 44
 and its properties, 41-45
 unsaturated, 473-487
 Carbon dioxide, 44
 additions to, 412-413
 Carbon disulfide, 412-413
 Carbon skeletons, 59-77, 163-164,
 Carbon tetrachloride, 44, 335
 Carbon-bromine bonds, 239, 241
 Carbon-carbon bonds, 117-118
 double, 333-334
 multiple, 314-327
 Carbon-chlorine bond, 242
 Carbon-halogen bonds, 124-127
 Carbon-heteroatom bonds, 124, 127,
 131-136, 155
 Carbon-hydrogen
 analysis for, 11-13
 combustion apparatus, 12
 Carbon monoxide, 121
 Carbon-nitrogen bonds, 124-127
 Carbon-oxygen bonds, 124-127
 Carbonic acid, 44, 82
 Carbonium ion, 222, 319
 dehydrohalogenations involving
 intermediates, 298-300
 rearrangements, 286-290, 511-514
 Carbonium-ion intermediate, 241, 242,
 243, 246
 Carbonium ion process, 263-266, 852-853
 competition between direct displacement
 and, 275
 Carbonyl dipole, 321
 Carbonyl halides, 121
 Carbonyl oxygen, 414-418

- 2-Carboxy-3-ketopentose-1,5 diphosphate, 726
 Carboxylate anions, 211
 Carboxylic acids, 82, 149, 151, 180, 514
 acidity in, 148-153
 malonic ester syntheses of, 463-466
 Carboxypeptidase, 741-742
 Carbylamine, 267
 Carotenes, 777
 Carothers, Wallace, 866
 Casein, 738
 Catalysis, 253-255
 acid, 254
 base, 254
 Catalytic cracking, 835
 Catalytic desulfurization, 834
 Cation-exchange resin, 867
 Cationic carbon, 247
 atom of, 266
 Cationic detergents, 765
 Cationic species, 314
 Cellobiose, 715
 Cellulose, 715-719
 Cellulose gum, 717-718
 Cephalins, 766-767
 Cetyl palmitate, 760
 Chain initiation, 850
 Chain length, 854-856
 Chain propagation, 850
 Chain reaction, 330, 539
 Chain termination, 851
 Chain transfer, 851
 Chalcone, 475
 Charles F. Kettering Foundation, 725
 Chelate, 796
 Chemical bonding, 20-53
 carbon and its properties in, 41-45
 molecular properties of, 36-41
 principles underlying, 20-36
 Chemical properties, fundamental, 117-157
 Chemisetting resins, 861
 Chemotherapy, 724, 827-831
 Cherry red, 663
 Chitin, 722
 Chloranil, 826
 Chlordan, 592
 Chlorides, 46
 acid, 379-380
 acyl, 450
 aryl, 423
 benzoyl, 452
 bornyl, 773
 ferric, 383
 isovaleryl, 440
 β -naphthoyl, 577
 neopentyl, 544
 picryl, 479, 480
 sulfenyl, 566
 Chlorine, 767
 Chloro IPC, 824
 Chloroacetic acid, 209
 Chloroamphenicol, 831
 chloroarenes, 271
 chlorobenzene, 155
 free energy diagram for, 360
 reactivity toward nitration, 354
 temperatures required to convert, 479
 2-Chloro-1, 3-butadiene, 323, 860
 2-Chlorocyclohexanone, 522
 Chloroethers, 332
 Chloroethylbenzene, 323
 Chlorohydrindene, 323
 Chlorohydrins, 242
 Chloroketones, 270
 Chloromethanes, 331
 Chloromethylbenzene, 354
m-Chlorophenylmethylcarbinol, 437
 Chlorophyll, 738
 Chlorophyll a, 807
 Chlorophyll b, 807
 Chloroprene, 323, 860
 Chloropropionitrile, 323
 Chlorosuccinic acid, 630
 Chlorosulfonation, 343
 Cholesterol, 778
 Cholic acid, 780
 Choline, 818
 Chromatography, 742-743
 Chromone, 799
 Chromonium ion, 800
 Chromonium salts, 800
 Chromophores, 650-652
 dyes classified according to, 654-657
 Chromoproteins, 738
 Cinerin I, 825
 Cinerin II, 825
 Cinnamaldehyde, 474-475
 Cinnamic acid, 333, 547, 459
 Cinnamone, 458
 Citric acid, 724
 L-Citrulline, 732
 Citrus bioflavonoid, 818
 Claisen ester condensation, 459-460
 reverse, 467
 Claisen rearrangement, 528-529
 Claisen-Schmidt reaction, 458
 Clathrate, 719
 Clemmenson reduction, 582
 Codeine, 167
 Coenzymes, 748-751
 Coenzyme-I, 749
 Coenzyme R, 818
 Colchicine, 823
 Collagen, 737
 Collision theory, 232

- Collodion, 716
 - Colloidal materials, 9
 - Color, 639-666
 - absorption of light and, 650
 - dyes, 652-660
 - emission and, 650
 - production of visible, 649-650
 - Combustion, 121, 550-552
 - Combustion tube, 12
 - Commoner, Barry, 725
 - Compounds
 - active hydrogen, 448-472
 - aromatic, 339-340
 - oxidation of, 555-556, 564-565
 - relative reactivities of, 354
 - azo, 498
 - cumulated unsaturated, 441
 - cyclic, 68
 - diazo, 495-509
 - diazonium, 495-509
 - epoxy, 438-439
 - halo-carbonyl, 451
 - infrared spectra in, 646-647
 - lipids, 766-767
 - lower valence, 585
 - meso*, 620
 - nitro, 585-586
 - nitrogen, 629
 - optical bleaches, 653
 - optically active, 626-631
 - organic peroxy, 568-570
 - organomercury, 424, 827
 - organometallic, 420-441
 - organophosphorus, 428
 - organosilicon, 841-846
 - polycyclic, 593-595
 - sandwich, 424-427
 - saturated, 65
 - silicon organic, 841-848
 - sulfur, 565-566
 - unique, 165-166
 - unsaturated, 65
 - hydrogenation of, 576-577
 - Condensations, 454-460
 - aldol, 457-458
 - aromatic ring, 460-463
 - benzoin, 492-493
 - Claisen ester, 459-460
 - reverse, 467
 - Perkin, 458-459
 - polymers, 865-868
 - reactants, 455-456
 - reversibility of reactions, 460
 - specific reaction mechanisms, 456
 - typical, 456-460
- Configurational formulas, 615-619
- Configurations, 18
 - of aldoses, 706-709
 - alpha, 714
 - determining, 680
 - electrons of unreactive elements, 23
 - inert gas, 24-25
 - Conformations, 18, 61-63
 - boat, 71
 - chair, 71, 73
 - determining, 680
 - skew, 64-65
 - transoid, 64-65, 68
 - twist, 71, 73
 - Congo red, 654
 - Coniferyl alcohol, 727
 - Coniine, 802
 - Conjugate acids, 283
 - Conjugate eliminations, 305
 - Conjugated proteins, 736-738
 - Conjugated systems, 67
 - additions to, 320-321
 - Conjugation, 140-155
 - electronic energy and, 645-649
 - in modifying acid strengths, 211-212
 - properties of, 184-195
 - Coordination, 229
 - Cope elimination reaction, 304
 - Copolymerization, 856-858
 - Copolymers, 856-858
 - Cordus, Valerius, 286
 - Coronene, 76-77
 - Cortisone, 781
 - Cotton, Aimé, 633
 - Cotton effect, 633-634, 637
 - Coumarin, 798, 799
 - Coupling, 433-434
 - azo, 347-348
 - dye, 497-499
 - free radical, 538
 - spin
 - interactions with two methyl groups, 673
 - with three identical hydrogens, 673
 - with two identical hydrogens, 673
 - Covalent bonding, 25-27
 - Crafts, James Mason, 344
 - Creatine, 804
 - Cresol, 81
 - p*-Cresol, 867
 - Crick, F. H. C., 813
 - Criegee reaction, 562-563
 - Cross-conjugated systems, 252
 - Crossed-Cannizzaro reaction, 489
 - Crotonaldehyde, 457, 458
 - trans*-Crotyl chloride, 273
 - Cryptoxanthin, 777
 - Crystal violet, 653
 - Cumene hydroperoxide, 541

- Cumulated systems, 67
 Cumulene, 67
 Cupric oxide, 176
 Curtius reaction, 312
 Curtius rearrangement, 514-515
 Cyanide, 87
 Cyanide ion, 267
 Cyano group, 276
 Cyanobenzyl alcohol, 276
 Cyanobenzyl chloride, 276
 Cyanoethylation, 474
 Cyanohydrins, 396-397
 formation of, 397
 Cyclic acetal, 478
 Cyclic anhydride, 250
 Cyclic compounds, 68
 Cyclic imides, 87
 Cyclic isomers, 74
 Cyclic polymers, 85
 Cyclization, 790
 reactions, 385-387
 Cycloadditions, 588-599
 bridged polycyclic compounds, 593-595
 cyclobutane ring formation, 595-596
 diene synthesis, 588-593
 Cycloalkanes, 120
 Cyclobutadiene, 145
 Cyclobutane rings, 69, 117-118, 595-596
 Cyclobutanediones, 596
 Cyclobutene, 595
 β -Cyclocitral, 772
 1,3-Cyclohexadiene, 589
 1,4-Cyclohexadiene, 584
 Cyclohexane, 120, 141, 142
 infrared spectra in, 646-647
 Cyclohexane ring, 68, 73
 conformations of, 71
 Cyclohexanone, 492
 stereochemistry of, 634-636
 Cyclohexatriene, 141
 Cyclohexene, 322
 Cyclooctatetraene, 145
 Cyclopentadiene, 592, 594
 Cyclopentadienide ion, 425
 Cyclopentane, 434
 Cyclopentane ring, 69
 Cyclopentanecarboxylic acid, 523
 Cyclopentanone, 470
 Cyclopentene, 315
 Cyclopropane, 306
 Cyclopropane rings, 69, 117-118, 307
 bond hybridization in, 119
 Cyclopropanone, 398
 L-Cysteine, 732
 L-Cystine, 732
 Cytidine, 812
 Cytosine, 811
 DL-2,3-Butanediol, 791
 DPN⁺, Coenzyme-1, 749
 Debyes, 192
 Decalins, 75-76
 Decarbonylation of aldehydes, 543
 Decarboxylation(s)
 reactions, 467-470
 typical, 469-470
 Degradation
 of aldoses, 699
 of fatty acids, 759-760
 of a porphyrin, 808
 of proteins, 741-742
 Ruff, 699
 Wohl, 699
 Dehalogenations, 300-301
 Dehydroascorbic acid, 819
 Dehydrogenation, 579
 Delocalization energy, 142-143, 145
 Denaturation, 736-737
 Denatured proteins, 738
 Deoxyribose, 813
 2-Deoxyribose, 710
 Deoxyribonucleic acids, 812-813
 Depolymerization, 543-544
 Depot fats, 759
 Derived proteins, 736-738
 Desulfurization, 834
 Detergents, 761-766
 cationic, 765
 colloid chemistry, 761
 manufacture of, 761-766
 molecules of, 761
 nonionic, 765
 Detonation, 550-552
 Developed dyeing, 659-660
 Dextrorotatory (clockwise), 67
 Diacetone alcohol, 299, 457
 Dialkyl amines, 219
 N,N-Dialkylamides, 440
 Dialkyloxonium ions, 283
 Diamminsilver ion, 156
 Diamond crystal lattice, 41-42
 Diaryl ethers, 221, 285
 Diastereoisomers, 619-620, 699
 1,3-Diazanaphthalene, 790
 1,4-Diazanaphthalene, 790
 1,3-Diazete, 787
 1,2-Diazine, 788
 1,4-Diazine, 788
 Diazo compounds, 495-509
 properties of, 501-505
 reactions of, 501-505
 Diazo hydrocarbons, 310
 Diazo hydroxide, 497
 Diazoamino compounds, 660
 Diazoate ion, 497

- Diazobornane, 514
 1,3-Diazole, 788
 Diazomethane, 310, 503
 Diazonium compounds, 495-509
 Diazonium ion, 527
 Diazonium salts
 properties of, 496-501
 reactions of, 496-501
 reduction of, 586
 Diazotype processes, 660
 Dibenzalacetone, 458
 Dibenzamide, 518
 Dibenzofuran, 789
 Dibenzo [b,d] furan, 789
 Dibenzo [b,e] pyran, 789
 Dibenzo [b,e] pyridine, 789
 Dibenzo [b,d] pyrrole, 789
 Dibenzylideneacetone, 458
 Dibromides, 270
 Dibromobutane, 169
 Dibromoethane, 187
 2,5-Dibromofuran, 795
 2,5-Dibromothiophene, 795
 Dichlone, 826
 Dichlorides, 270
 Dichloroacetic acid, 209
o,o-Dichlorobiphenyl, 622
 2,2'-Dichloro-6-bromobiphenyl, 621
 Dichlorocarbene, 308-309
 Dichlorochlorovinylarsine, Lewisite, 829
 Dichlorocyclohexane, 75
 Dichlorocyclopropanes, 309
 Dichlorodifluoromethane, 848
 Dichloroethane, 247-248
 conformations of, 249
 Dichloroethylene, 18
 Dichloromethylene, 308
 2,4-Dichlorophenol, 481
 2,4-Dichlorophenoxyacetic acid, 823
 Dicoumarol, 798
 Dicyclohexylcarbodiimide, 747
 Dicyclopentadiene, 592
 Dieckmann cyclization, 460
 Dieldrin, 592
 Dielectric constants, 255
 Diels, Otto, 588
 Diels-Alder reaction, 589
 of cyclopentadiene, 594
 reversibility of, 590
 typical, 591-593
 Diene, 320
 Diene synthesis, 588-593
 Dienophiles, 588
 Diethanolamine, 791
 Diethyl ether, 286
 Diethylacetal, 400
 Diethyldichlorosilane, 427, 842
 Diethylene dioxide, 788
 Diethylene glycol, 791
 Diethylstilbestrol, 782, 783
 Diffraction, 684-688
 electron, 688
 neutron, 688
 patterns in, 686
 techniques, 687-688
 theory of, 684-687
 x-ray, 687-688
 Difluorochloromethane, 848
 Digestion, 722-724
 Dihalocarbenes, 308
 Dihedral angle, 63
 9,10-Dihydroanthracene, 584
 9,10-Dihydroanthracene-9,10-*endo*-succinic anhydride, 593
 Dihydrofuran, 796
 9,10-Dihydro-10-oxanthracene, 789
 Dihydroxyacetone phosphate, 723, 726
 β,δ -Dihydroxy- β -methylvaleric acid, 779
 Diiodides, 316
 Diisobutylene, 838
 Diketopiperazine, 735
 Dimeric amides, 181
 Dimethyl sulfoxide, 296
 Dimethylacetamide, 186
 Dimethylacetylene, 68
 γ -Dimethylallyl pyrophosphate, 779
 4-Dimethylaminoazobenzene, 498
N,N-Dimethylaniline, 501
 2,3-Dimethylbutadiene, 860
 2,2-Dimethylbutane, 836
 Dimethylcyclopropane, 74-75
 Dimethyldichlorosilane, 427, 842
 2,2-Dimethyldioxolane, 400
 Dimethylethylamine, 303
 Dimethylformamide, 275, 278
 2,2-Dimethylbutane, 836
 3,3-Dimethylpentane, 836
 Dimethylpropylamine, 303
 5,8-Dimethyltol, 819
 7,8-Dimethyltol, 819
m-Dinitrobenzene, 480
 2,4-Dinitrochlorobenzene, 479, 480
 2,4-Dinitrofluorobenzene, 481
 Dinitrophenol, 212
p-Dioxane, 788
 1,4-Dioxane, 788
 Dipeptide hydrochloride 735
 Diphenyl ether, 155
 Diphenylamine, 219, 221
 Diphenylcarbene, 308
o-Diphenylene, 485
 Diphenylpicrylhydrazyl, 536
 1,3-Diphosphoglyceric acid, 723
 Diphosphopyridine nucleotide, 749

- Dipolar aprotic solvents, 275
 Dipole moments, 32, 184, 187, 192-195
 of benzene, 352
 in determining structure, 680-682
 electric, 676-683
 of methane, 352
 structure and, 676-682
 Dipropyl, 286
 Diradicals, 545-547
 Direct dyeing, 659
 Disaccharides, 712-715
 digestion of, 722-724
 Dispersion, 605
 optical rotatory, 633-638
 Displacement process, direct, 262-263
 competition between carbonium ion process
 and, 275
 Dissociation constants
 for acids, 212
 for monosubstituted benzoic acids, 215
 Dissociation energies, 226
 Diterpenes, 776-777
 Dithiocarbamates, 826
 1,2-Dithioglycerol, 829
n-Docosane, 543
 2-Dodecenedioic acid, 822
 Dodecyl alcohol, 583
 Dow processes, 155
 Dumas, J. B. A., 6
 Dumas gasometric method, 13
 Duren sulfonic acid, 524
 Dye coupling, 497-499
 Dyeing, 652-660
 developed, 659-660
 direct, 659
 ingrain, 659-660
 mordant, 659
 Dyes, 652-660
 acid, 654, 655
 azine, 656
 azo, 654
 basic, 655
 classified according to chromophores,
 654-657
 indigoid, 657
 nitro, 656
 phthalein, 655-656
 quinone, 657
 sulfur, 657
 triphenylmethane, 655-656
 vat, 657, 660
 xanthene, 801
 Eclipsing strain, 69, 73
 Elastin, 737
 Electric dipole moments, 676-683
 Electrolyte, 206
 Electromagnetic absorption spectra, 185-189
 Electromagnetic waves, 640
 Electron-deficient rearrangements, 510-522
 Electronic energy, 645-649
 Electronic formulas, 17-18
 Electron-rich rearrangements, 510, 522-523
 Electrons, 20-24
 configurations of unreactive elements, 23
 diffraction, 32, 688
 oxidation of, 46-47
 pair bonds, 17
 pairs, unshared, 122-124
 paramagnetic resonance, 674-675
 quantum numbers of, 21
 reduction of, 46-47
 transfer, 229
 unpaired, 532
 Electrophiles, 123
 types of, 243-245
 Electrophilic additions
 to carbon-carbon multiple bonds, 314-327
 mechanisms of, 315-317
 Electrophilic aromatic substitution, 338-370
 nature of, 338-339
 orientation with several groups, 360
 representative reactions, 362-367
 reversibility in, 361-362
 side reactions, 367-368
 substituent effects, 348-362
 Electrophilic reagents, 130, 147, 338, 340-348
 Electrophoresis, 734
 Electrovalence, 24-25
 Elimination reactions, 292-312
 alpha, 308-312
 base-promoted, 293-295, 297-298
 beta, 292-303
 conjugate, 305
 Hofmann, 292, 301-303
 involving internal replacements, 306-307
 pyrolytic, 304-305
 reagents for, 296-297
 Empirical formulas, 6, 14
 Enantiomorphous allenes, 621
 Enantiomorphs 67, 79, 615, 622
 Endergonic system, 235
 Endo alcohol, 594
 Endopeptidases, 742
 Endothal 824
 Energy
 changes in molecules, 639-641
 electronic, 645-649
 molecular ionizing, 691-692
 Enol, 172
 Enolate ion, 150, 211, 448-472
 Enolpyruvic acid, 723

- Enols, 150, 152, 448-472
 Entropy, 237
 Enzymes, 748-751
 neutralizers, 829
 Eosin, 656
 Epichlorohydrin, 307, 325
 Epimers, 699
 Epinephrine, 821
 Epoxidation, 569-570
 reaction, 552
 Epoxides, 242, 277, 306
 Epoxy compounds, 438-439
cis-2,3-Epoxybutane, 791
 Equatorial groups 74
 Equilenin, 782
 Equilibria, quantitative treatment of, 236-240
 Equilibrium constants, 229-230
 Eremophilone, 774
 Ergosterol, 547, 781
 Eriodictiol, 818
 Erlenmeyer structures, 172
 Erythro configurations, 617
 Erythrose-4 phosphate, 726
 D-Erythrose, 707
 Esterification reaction, 133
 Esters, 84, 261
 acetoacetic
 dialkylated, 466
 monoalkylated, 466
 syntheses, 466-467
 Claisen condensation, 459-460
 enol of, 450
 glyceryl, 135
 hydrolysis of, 376-378
 alkaline, 378-379
 interchange as a nucleophilic displacement,
 373-375
 malonic syntheses, 463-466
 of methacrylic acid, 406
 sodium malonic, 464
 structures by cleavage and synthesis, 166-168
 sulfonate, 385
 of tertiary alcohols, 388
 thiol, 280
 unhydrolyzed, 379
 unsaturated
 additions to, 474-476
 polymers from, 863
 with active hydrogen, 455
 Estradiol, 782
 Estrone, 781
 Étard method, 560
 Ethane, 36-37, 59-60
 conformations of, 248
 energy diagram for rotation of, 63
 Ethano bridges, 76
 Ethanol, 18, 166, 267, 324
 NMR spectrogram of, 670, 671
 Ethanolamine, 767, 791
 Ethanolic alkali, 295
 Ethanolic sodium hydroxide, 293
 Ether, 81, 179, 261
 allyl isopropenyl ether, 529
 ethyl vinyl, 433
 insoluble, 122
 structures of cleavage and synthesis, 166-168
 tert-butyl methyl, 384
 Ethyl acetate, 490
 Ethyl acetoacetate, 454, 466
 Ethyl adipate, 576
 Ethyl alcohol, 454
 Ethyl benzoate, 354
 Ethyl bromide, 334
 Ethyl bromoacetate, 438
 Ethyl bromozincacetate, 438
 Ethyl cellulose, 717
 Ethyl cinnamate, 477
 Ethyl cyanoacetate, 477
 Ethyl 2-cyclopentanonecarboxylate, 460
 Ethyl hydrogen sulfate, 217
 Ethyl iodide, 92
 Ethyl laurate, 583
 Ethyl malonate, 463, 477
 Ethyl malonate enolate ion, 463
 Ethyl *N*-methyl-*N*-nitrosocarbamate, 495
 Ethyl octadecanedioate, 543
 Ethyl phenylcyanoacetate, 464-465
 Ethyl vinyl ether, 433
 Ethylbenzene, 836
 Ethylcadmium bromide, 440
 Ethylene, 34-35, 147, 334
 Ethylene glycol, 791
 Ethylene oxide, 170, 787, 791
 Ethylenimine, 787
 2-Ethylhexyl phthalate, 864
 Ethylidene chloride, 171
 3-Ethylpentane, 836
 Ethylpropyldimethylammonium hydroxide,
 303
 Ethyltrichlorosilane, 427, 842
 Ethynylation, 397-398
 Eudalene, 775
 Eudesmol, 774
 Eugenol, 167
 Exergonic system, 235
 Exo alcohol, 594
 Exothermic reactions, 237
 Explosion, 550-552
 FAD, 749-750
 FMN, 749-750
 Farnesol, 774

Farnesyl pyrophosphate, 779

Fats

- acids from, 757
- analytical values of, 755
- biological utilization of, 759
- chemical properties, 754-756
- depot, 759
- hydrolysis of, 754-755
- physical properties, 754
- structure, 756-758

Favorsky rearrangement, 522-523

Fehling's solution, 698

Fermentation process, 81

Ferric chloride, 383

Ferric cytochrome, 749

Ferric ion, 152

Ferrocene, 424-425

Ferrous hydroxide, 156-157

Fibroin, 737

Fischer, Emil, 634, 704, 706

Fischer, Hans, 808

Flavinadeninedinucleotide, 749-750

Flavinmononucleotide, 749-750

Fleming, Alexander, 83

Fluid catalytic cracking, 835

Fluorene, 433

9-Fluorenylmagnesium halide, 433

Fluorescein, 655

Fluorescence, 652

- energy transitions leading to, 658-659

Fluorine, 124, 332

Fluorocarbons, 848

Fluorochlorobromomethane, 79

Folic acid, 816

Folinic acid, 751

Formaldehyde, 47, 171

Formic acid, 83-84, 165, 210

Formulation, 11-18

- determination of composition, 11-13
- qualitative analysis, 11

Frankland, Edward, 3

Free radicals, 226, 532-549

- diradicals, 545-547
- energy requirements of, 334-335
- evidence for, 533-536
- formation of, 537-538
- fragmentation of, 542-544
- initiation of, 537-538
- ions, 545
- nature of, 532-533
- processes, 329-330, 850-852
- reactions, 538-542
- rearrangements, 544-545
- stereochemistry in, 542
- See also* Radicals

Freezing point, 7

Friedel, Charles, 344

Friedel-Crafts reactions, 344-347, 528, 529

Fries rearrangement, 528

Fructose, 709

Fructose-1,6 diphosphate, 723, 726

Fructose-6 phosphate, 723, 726

α -D-Fructofuranose, 705

β -D-Fructofuranose, 705-706

Fuchsin, 655

Fulvenes, 252

Fumaric acids, 250, 724

Functional group, 163

Functional isomers, 169-170

Fungicides, 826-827

Furan, 791, 795

Furfural 792

Fused aromatic systems, 145

Gabriel synthesis, 278

D-Galactose, 707

Galacturonic acid, 721

Gamma position, 210

Gattermann, Ludwig, 499

Gattermann's modification, 499-500

Geometric isomers, 39-40, 66, 74

Geranial, 772

Geranyl pyrophosphate, 779

Gliadin, 737

Globin, 737

Globulins, 737

Glucaric acid, 698

Gluconic acid, 698

α -D-Glucopyranose, 706

2-Glucosamine, 722

Glucose, 91

- details of the molecule of, 701-704

- mutarotation of, 702

- as a typical monosaccharide, 696-699

D-Glucose, 707, 709

Glucose-1 phosphate, 723

Glucose-6 phosphate, 723, 726

Glucuronic acid, 698

L-Glutamic acid, 733

L-Glutamine, 732

Glutelins, 737

Glutenin, 737

Glycaric acid, 698

D-Glyceraldehyde, 707

(S)-Glyceraldehyde, 625

Glycerol, 92

Glycerol dichlorohydrin, 307

Glyceryl esters, 135

Glyceryl- α -palmitate- α' , β -distearate, 758

Glyceryl tristearate, 758

Glycine, 732

Glycocholic acid, 781

- Glycogen, 723
 digestion of, 722-724
 Glycols, 80
 hexamethylene, 576
 Glycoproteins, 737
 Glycosides, 711-712
 naturally occurring, 711
 Glyoxal dihydrate, 399
 Glycuronic acid, 698
 Golden yellow, 663
 Gomberg, Moses, 532
 Graphite, 42-43
 crystal lattice, 42-43
 electron transfer in, 43
 Greek letter conventions, 97
 Green
 emission and absorption relationships, 650
 malachite, 653, 655
 Grignard, Victor, 422
 Grignard reaction, 127, 422
 Grignard reagents, 422-423
 acid derivatives and, 439-440
 aldehydes and, 437-438
 aryl, 431
 carbonation of, 441
 ketones and, 437-438
 syntheses by addition, 436-437
 Group interactions, 139-157
 conjugation and resonance, 140-155
 oxidation and reduction, 155-157
 Guaiazulene, 775
 Guaiol, 774
 Guanidines, 222
 Guanidinium ion, 252
 Guanine, 811
 Guanylic acid, 812
 D-Gulose, 707

 Halide, 78-79
 acyl, 84
 alkyl, 78, 123, 126-127
 aryl, 126-127
 carbonyl, 121
 coupling of, 433
 nucleophilic displacements in, 481-482
 phosphorus, 290
 poly, 78
 replacements of, 260-280
 side reactions of, 279-280
 vinyl, 129
 Halide ion, 284
 Halo-carbonyl compound, 451
 Haloethylene polymers, 863
 Haloform reaction, the 452-454
 Halogen acids, 284
 Halogen atoms, 155

 Halogenation, 78, 154, 452
 and addition to olefins by free radical processes, 329-336
 acid-catalyzed, 450-452
 reactions, 362-363
 reagents for, 340-342
 Halogens, 52, 120, 121, 209
 replacement by metal, 422-423
 Haloketones, 294
 Hantzsch synthesis, 796, 798
 Haworth, W. N., 702
 Heisenberg uncertainty principle, 20
 Helindon yellow CG, 657
 Helium atom, 25
 Hell-Volhard-Zelinsky reaction, 450-451
 Hemiacetal, 702
 formation of, 398-401
 Hemicelluloses, 721
 Hemoglobin, 738
 Heptachlor, 593
 Heptane, 836
 Heptanoic acid, 699
 Heteroauxin, 822
 Heterocycles, 785-814
 bridged polycyclic, 802-804
 chemical properties of, 793-796
 nomenclature, 786-790
 occurrence, 785-786
 physical properties of, 793
 suffixes of simple, 786
 syntheses, 790
 with more than one hetero atom, 804-806
 Heterolysis, 229
 Heterolytic reagents, 243
 Heterolytical, 263
 γ -(meso) Hexachlorocyclohexane (lindane), 621
 Hexachlorocyclohexanes, 336, 621
 Hexachlorocyclopentadiene, 592
 1,7,8,9,10,10-Hexachlorotricyclo (5.2.1.0^{2,6})
 decane, 592
 Hexamethylbenzene, 687
 Hexamethylene glycol, 576
 Hexamethylenediamine, 381, 577, 866
 Hexane, 836
 Hexanedione, 186
 Hexatriene, 320
 1-Hexene, 836
 Hexoses, 707
 Hexyl bromide, 155
 Hibbert method, 299
 Hinsberg, O., 388
 Hinsberg test, 388
 Hippuric acid, 381
 L-Histidine, 732
 Histones, 737

- Hofmann, August W., 302
 Hofmann elimination reactions, 292, 301–303, 304
 Hofmann rearrangement, 311, 514–515
 Hofmann synthesis, 278
 Holoenzymes, 748
 Homologous series, 59
 Homologs, 78
 refractions of, 607
 Homology, principle of, 59, 166
 Homolysis, 226, 537
 Homolytic process, 329–330
 Hordein, 737
 Hormones, 781–782, 815–825
 plant, 822
 Hückel's rule, 145
 Hybrid orbitals, 32–34
 Hydrated ferric oxide, 156
 Hydrates, formation of, 398–401
 Hydrazine, 135
 Hydrazobenzene, 527, 583
 Hydride, 443–445
 lithium aluminum, 442–444
 metal
 handling hazards, 445
 reduction by, 441–445
 Hydride exchange, 488–494
 Hydrobenzamide, 418
 Hydroboration, 427–428
 Hydrobromic acid, 45, 285
 Hydrocamphenyl cation, 773
 Hydrocarbon groups, 104–107
 Hydrocarbon(s), 77
 formulas and structures of, 14
 molecules, 183
 saturated, 556
 unsaturated
 hydrogenation of, 574–576
 oxidation of, 552–554
 Hydrochloric acid, 218, 284
 Hydrochloride, 773
 Hydrogen
 bonds to, 118–122
 active
 anhydride with, 455
 reactions of, 448–472
 ester with, 455
 ketone with, 455
 coupling with, 673
 molecule, 25
 reactions, conditions of, 572
 Hydrogen bonding, 40–41, 179
 Hydrogen bromide, 257
 Hydrogen fluoride, 284
 Hydrogenation, 572–580
 of polar unsaturated compounds, 576–577
 of unsaturated hydrocarbons, 574–576
 Hydrogenolysis, 572–580
 Hydrohalogen acids, 290
 Hydroindigo, 657
 Hydrolipoic acid, 726
 Hydrolysis
 amide formation and, 380–383
 of cellulose, 718
 of esters, 376–378
 alkaline, 378–379
 sulfonate, 385
 of fats, 754–755
 of oils, 754–755
 of pentamethylglucose, 704
 of proteins, 740
 of sucrose, 713
 Hydroperoxide, 541
 Hydroperoxide formation, 540–541
 Hydroquinone, 156–157
 Hydroxamic acids, 382–383
 Hydroxide ion, 135, 151, 242
 Hydroxy, 78
 Hydroxy compounds, 276
 Hydroxy group, 133, 283
 Hydroxyaldehyde, 702
p-Hydroxyazobenzene, 498
 Hydroxybenzoic acid, 216
 Hydroxylamine, 135
 Hydroxylation, 569–570
 β -Hydroxy- β -methylglutaryl, 779
 L-Hydroxyproline, 732
 8-Hydroxyquinoline, 796
 Hyperconjugation, 269
 Hypochlorous acid, 325
 Hypoxanthine, 811
 Hypsochromes, 650–652

 D-Idose, 707
 Imidazole, 788, 804
 Imides, 86–87
 orbital formula for, 154
 Imidol, 516
 Imines, 136
 Imino tautomer, 252
 Immersion refractometer, 604
 Indicators, 660–663
 pH Indicators, 660–663
 Indigo, 657
 Indigoid dyes, 657
 Indole, 789, 791
 Indole-3-acetic acid, 822
 δ -Indole-3-butyric acid, 823
 Indoxyl, 793
 Inductive effect, 208–209
 as measured by acid strengths, 209
 Inductive release, 269
 Inert gas configurations, 24–25
 Infrared spectra, 644–647

- Ingrain dyeing, 659-660
 Initiators, 330
 Inorganic reagents, 45-53
 acids, 45
 bases, 46
 Inositol, 767, 818
 Insecticides, 825-826
 Insulin, 743, 821
 Internal return, 274
 Intramolecular reactions, 248-251
 Invert soaps, 765
 Iodide ion, 240
 Iodides, 179, 422-423
 Iodine numbers, 755
 Iodobenzene, 354
 Ion beams, positive, 689
 Ion pair, 264-266
 intimate, 265
 solvent-separated, 266
 tight, 265
 Ion-dipole, 316
 Ionic reagents, types of, 243-245
 Ionic species, 223
 Ionization constants, 208
 Ions, 24-25
 dissociated, 266
 radical, 545
 Isatin, 785
 Isobornyl chloride, 773
 Isobutane, 16-17, 60
 mass spectrum of, 691
 Isobutyl adipate, 864
 Isobutyl alcohol, 288
 Isobutyl bromide, 288
 Isobutylene, 428, 838, 852
 Isocitric acid, 724
 Isocyanate, 311
 cumulated unsaturated system of, 407-414
 preparation of, 409-410
 Isocyanides, 310
 Isoelectric point, 734
 Isoindole, 789
 L-Isoleucine, 732
 Isomerization, 839
 Isomers, 16
 cyclic, 74
 formation of, 589-591
 functional, 169-170
 geometric, 66, 74
 number methods, 172-175
 optical, 615
 physical properties of, 622-625
 positional, 79
 skeletal, 60
cis-trans Isomers, 66, 248-251, 645
 determination of, 680
 Isonitrile, 267
 Isopentane, 60
 Isoprene, 770, 858
 Isopropyl alcohol, 163, 168, 294, 324
 Isopropyl bromide, 163
 Isopropyl N-phenylcarbamate, 824
 Isoquinoline, 789, 796
 Isosteres, 795
 Isotactic polymers, 854
 Isothiocyanates, 441
 cumulated unsaturated system of, 407-414
 Isovaleryl chloride, 440

 Jacobsen rearrangement, 523

 Katsoyannis, P. G., 744
 Kekulé, Friedrich August, 3, 15
 Kekulé structures, 141, 142, 143, 172, 362
 Keratin, 737
 Ketenes
 cumulated unsaturated system of, 407-414
 preparation of, 409-410
 Keto form, 150
 α -Ketoglutaric acid, 724
 Ketoketenes, 410
 Ketol, 299
 Ketones, 82
 acetoacetic ester syntheses of, 466-467
 addition products of, 396-407
 enol of, 450
 Grignard reagents and, 437-438
 reactions of, 392-419
 unsaturated, 474-476
 with active hydrogen, 455
 Ketonic oxygen, 132
 Kiliani, Heinrich, 699
 Kiliani synthesis, 699, 707
 Kinetic collision rate, 232
 Kjeldahl titrimetric method, 13
 Knock ratings, 835
 Kolbe, Hermann, 3
 Kolbe synthesis, 543
 Korner-Griess-Salkowsky method, 174

 Lactalbumin, 737
 Lactams, 385-387
 Lactones, 385-387
 α -Lactose, 715
 Lanosterol, 777, 778, 779
 Lavoisier, Antoine, 11
 Leaving groups, 261
 LeBel, Joseph, 79
 Lecithins, 766-767
 L-Leucine, 732
 Leucoindigo, 657
 Levorotatory (counterclockwise), 67
 Levulinic acid, 859
 Lewis, Gilbert N., 207

- Lewis acids, 118, 244, 254, 275, 284, 298, 322, 329
 Lewis base, 218, 244, 260
 Lewis theory, 207, 244
 Lewisite, 422
 Liebig, Justus von, 11, 226
 Light
 absorption of, 633
 color and, 650
 law of, 643-644
 spectra and, 639
 by vibrational transition, 642
 wavelength, 649
 action of two Nicol prisms on, 612
 plane-polarized, 609
 rotation of, 613
 polarized, 609-611
 theory of refraction of, 603-604
 Light waves
 perpendicular vibrations of, 610
 vibrations of, 609
 Lignin, 725
 Limonene, 772
 Lindane, 336
 Linoleic acid, 756
 Linolenic acid, 756
 L-iodogorgoic acid, 732
 Lipids, 754-760
 compound, 766-767
 Lipoic acid, 726
 Lipoproteins, 738
 Lithium aluminum hydride, 442-444
 Lossen rearrangement, 514-515
 Lowry, T. M., 205
 Lucas' reagent, 284
 L-Lysine, 732
 D-Lyxose, 707

 Magenta, 655
 Magnesium, 149
 Magnetic quantum number, 21
 Magnetic resonance, 667-675
 detecting, 668-669
 measuring, 668-669
 Magnetic resonance spectrometer, 668-669
 Malachite green, 462, 653, 655
 Malaprade reaction, 562
 Malathion, 826
 Maleic acids, 250
 Maleic anhydride, 250, 555, 588
 Maleic hydrazide, 824
 Malic acid, 630, 724
 Malonic ester syntheses, 463-466
 Maltase, 714
 Maltose, 712
 Mandelic acid, 629

 D-Mannose, 707
 Markovnikoff, Vladimir, 318
 Markovnikoff's rule, 257, 318-320, 345
 Mass action, principle of, 230
 Mass spectra, 689-692
 Mass spectrometer, 9-10, 689
 Mass spectroscopy, 692
 Mauveine, 656
 Meerwein-Ponndorf-Verley reaction, 490-492
 Melamine, 868
 Melting point, 179
 of continuous-chain organic compounds, 182
 Menthol, 772
 Mercaptans, 124, 278, 335
 Mercuric sulfate, 324
 Mercurochrome, 424
 Merthiolate, 424
 Mesityl oxide, 299, 457
 Mesitylene, 458
 Meso compound, 620
 Mesomeric structure, 172
 Mesomers, 144
 Meta anion, 211
 Metabolite antagonists, 829
 Metaldehyde, 403
 Metal(s)
 hydrides, 441-445
 reduction by, 580-585
 with several valences, 585
 Metaphen, 424
 Metaproteins, 738
 Methacrolein, 51-52
 Methane, 45
 chlorination of, 330-331
 dipole moments of, 352
 Methano bridge, 76
 Methanol, 45, 47, 210
 L-Methionine, 732
 Methoxide ion, 273
 Methoxy, 209, 285
 Methoxyl, 215
 Methyl acetimidate, 186
 Methyl alcohol, 166
 Methyl alkylcarbinol, 454
 Methyl aryl ethers, 285
 Methyl benzoate, 384
 Methyl benzylidenemalonate, 476
 Methyl benzylmalonate, 476
 Methyl bromide, 239, 240
 Methyl cellulose, 717
 Methyl chloride, 330
 Methyl *cis*-cinnamate, 588
 Methyl *trans*-cinnamate, 588
 Methyl crotyl ether, 273
 Methyl ether, 166
 Methyl glucoside, 561

- Methyl groups, coupling with, 673
- Methyl halide, 268
- Methyl iodide, 167
- Methyl 3-methyl-3-cyclohexenecarboxylate, 591
- Methyl 4-methyl-3-cyclohexenecarboxylate, 591
- Methyl orange, 661, 663
- Methyl rubber, 860
- Methyl sulfate, 286
- Methyl terephthalate, 865
- Methyl violet, 662
- Methylallyl alcohol, 51-52
- Methylallyl chloride, 273
- Methylamine, 584
- Methylation, 361
- 3-Methyl-3-butenyl pyrophosphate, 779
- trans*-2-Methylcyclohexanol, 428
- Methylcyclohexene, 299
- 1-Methylcyclohexene, 428
- Methylene, 308-312, 565
- Methylene blue, 663
- 3-Methylenecyclohexene, 589
- 1-Methylglucuronic acid, 561
- 2-Methylheptane, 836
- 3-Methylhexane, 836
- 3-Methyl-3-hexanol, 438
- 5-Methyl-3-hexanone, 440
- 3-Methylidenecyclohexene, 589
- 2-Methyl-1, 4-naphthoquinone, 820
- p*-Methylolphenol, 461
- 2-Methylpentane, 836
- 3-Methylpentane, 836
- 2-Methyl-1-pentene, 836
- 2-Methyl-2-pentene, 836
- 8-Methyltolcol, 819
- Methyltrichlorosilane, 427, 842
- Methyltriphenylphosphonium iodide, 429
- Mevalonic acid, 779
- Meyer, Victor, 6, 785-786
- Michael addition, 476-477
- Midgley, Thomas, Jr., 424
- Millon's reagent, 740
- Molecular energy levels, 31
- Molecular formulas, 14-17
- Molecular geometry, 246-251
- Molecular ionizing energies, 691-692
- Molecular mass spectra, 690-691
- Molecular moments, 676-679
- Molecular motions, 641
- Molecular orbitals, 30-36
- Molecular polarity, 40
- Molecular properties, 36-41
 - geometry of, 36-38
 - hydrogen bonding, 40-41
 - polarity, 40
 - rotations in, 38-40
- Molecular rearrangements, 510-531
 - aromatic, 523-529
 - classification of, 510-511
 - electron-deficient, 510-522
 - electron-rich, 510, 522-523
- Molecular spectra, 639-652
- Molecular weights, 6-10
 - cellulose, 716
 - determination of, 6
 - from freezing and boiling points, 6-9
 - from mass spectrometer, 9-10
 - from nuclear magnetic resonance, 10
 - of porphyrins, 808
 - from spectroscopic data, 10
 - from vapor density, 6
 - from x-ray diffraction, 10
- Molecules
 - absolute configurations, 634
 - asymmetric, 620-622
 - of detergents, 761
 - effect of temperature on activation of, 232
 - energy changes in, 639-641
 - glucose, 701-704
 - of oxygen, 540
 - permanent inductive polarization in, 209
 - polar, 676
 - projections onto plane surfaces, 616
 - rotations in, 38-40
- Molozonides, 553
- Monoalkyl ether, 791
- Monoglyceride, 766
- Monomeric form, 181
- Monosaccharides, 695-711
 - chemical properties of, 696-699
 - classification of, 695
 - cyclic formulas for, 704-706
 - importance of, 709-710
 - interconversions, 699-701
 - physical properties of, 695-696
- Monoterpenes, 770-774
- Mordant dyeing, 659
- Morphine, 797, 803
- Mucin, 737
- Mucoids, 737
- Multiple bonds, 33-35, 65-68
 - general reactivities of, 314
- Mutarotation, 702
- Myogen, 737
- Myosin, 737
- Myrcene, 772
- Myricyl palmitate, 760
- NMR spectra, 669-674
- Names, common
 - additive, 95

- Names, common (*continued*)
 constitutive, 94-95
 derivative, 95
 generic, 95
 substitution, 95
 β -Naphthaldehyde, 577
 Naphthalene, 76, 145, 172
 β -Naphthaleneacetic acid, 530
 Naphthalene-1-acetic acid, 823
 α -Naphthalenesulfonic acid, 524
 β -Naphthalenesulfonic acid, 524
 Naphthol, 152
 β -Naphthol, 527
 β -Naphthoyl chloride, 577
 β -Naphthylthioacetomorpholide, 530
 Natta, Giulio, 854
 Neo carbon atom, 288
 Neopentane, 60
 Neopentyl alcohol, 288, 489
 Neopentyl bromide, 289
 Neopentyl cation, 511-512
 Neopentyl chloride, 512, 544
 Neophyl radicals, 544
 Neoprene, 860
 Neral, 772
 Neutron diffraction, 688
 Newman projections, 62, 617
 Niacin, 816
 Nicol prisms, 610-611, 612
 Nicotine, 175-176, 797
 Nicotinic acid, 175-176, 816
 Nickel, Raney, 574-575
 Ninhydrin, 740
 reaction, 740
 Nirenberg, M. W., 813
 Nitration, 154, 540
 reactions, 363
 reagents for, 342-343
 Nitric acid, 53, 117
 Nitrile, 87, 136, 267, 440-441
 addition to, 403-406
 addition products of, 396-407
 reactions of, 392-419
 Nitrite esters, 267
 Nitro compounds, 87, 169
 Nitro dyes, 656
 Nitroaniline, 194-195, 219
 Nitrobenzene, 194, 351-353
 absorption spectra of, 652
 free energy diagrams for, 356
 reactivity toward nitration, 354
 o-Nitrobenzenesulfonyl chloride, 566
 m-Nitrobenzoic acid, 504
 Nitrocellulose, 716
 m-Nitrochlorobenzene, 479
 o-Nitrochlorobenzene, 479
 p-Nitrochlorobenzene, 479
 Nitrogen
 analysis for, 13
 atoms, 121, 152, 169
 compounds, 629
 Dumas train, 13
 eliminations of, 505-507
 functions, 86-88
 Kjeldahl titrimetric method, 13
 migrations, 514-519
 Nitromethane, 351-353, 584
 Nitrophenol, 211
 m-Nitrophenylacetic acid, 504
 p-Nitrophenylvinyl bromide, 481-482
 Nitrosation, 348
 Nitrosoalkylureas, 495
 Nitrosoalkylurethanes, 495
 Nitrosoamines, 500
 Nitrosobenzene, 583
 p-Nitroso-N,N-dimethylaniline, 501
 Nitrous acid, 500-501
 Nobel, Alfred, 551
 No-bond resonance, 269
 Nomenclature, 91-112
 chemical abstracts, 104
 examples in representative classes of compounds, 110-112
 tables, 104-112
 Nonaromatic diene, 147
 Nonbonding interactions, 37
 Nonionic detergents, 765
 Norbornadiene, 592
 Norbornane, 75-76, 594-595
 Norbornene, 627, 806
 Norepinephrine, 822
 Norethynodrel, 783
 L-Norleucine, 732
 Nucleic acids, 810, 812-813
 Nucleophiles, 123-124, 125
 types of, 243-245
 Nucleophilic additions, 371-419
 general mechanisms for, 392-396
 in unsaturated systems, 436-447
 Nucleophilic agents, 260-261
 Nucleophilic displacement(s), 371-419
 aromatic, 478-481
 via aryne intermediates, 482-486
 ester interchange as a typical, 373-375
 reactions, 260, 371-373
 Carbonium-ion process, 263-266
 direct process, 262-263
 mechanisms of, 262-263
 role of metal ions in, 266-267
 in unsaturated systems, 436-447
 in vinyl halides, 481-482
 Nucleophilic reactions, 473-487

- Nucleophilic replacements**, 282-290
Nucleoproteins, 737
Nucleosides, 812
Nucleotides, 812
Nylon 66, 381, 866
- Ocimene**, 772
Octane, 836
Octane numbers, 835, 836
Octant rule, the, 635
1-Octene, 836
Oils
 biological utilization of, 759
 chemical properties of, 754-756
 hydrolysis of, 754-755
 physical properties of, 754
 silicone, 846
Oleanolic acid, 777
Olefinic bonds, 129-130
Olefins, 65, 92, 222, 287, 298
 addition to, 502-503
 structures, 168-169
Oleic acid, 756
Oligosaccharides, 715
Oppenauer reaction, 490-492
Optical activity, 609-632
 active substances, 611-613
 asymmetric carbon atoms, 619-620
 asymmetric molecules, 620-622
 conventions for configurational formulas, 615-619
 molecular basis of, 613-615
 physical properties of isomers, 622-625
 polarized light, 609-611
 preparation of compounds, 626-631
 racemic modifications, 620
Optical bleaches, 652
Optical configurations, 706-709
Optical isomerism, 67
Optical isomers, 615
 physical properties of, 622-625
Optical rotatory dispersion, 633-638
 applicability of, 638
 Cotton effects, 633-634, 637
 measurement of, 634
 structure and, 634-638
Orange
 emission and absorption relationships, 650
 methyl, 661, 663
Orbital formulation, 36
Orbital hybridization, 31-33
Orbitals
 atomic, 140, 142
 sigma molecular, 140
Organic compounds
 acidity and basicity in, 205-223
 classification of, 77-88
 constitution of, 59-88
 functional groups of, 77-88
Organic molecules, 184
Organic peroxides
 compounds, 568-570
 preparation of, 568-569
Organomagnesium halides, 422
Organomercury compounds, 424, 827
Organometallic compounds, 127, 420-435
 chemical reactions, 431-434
 handling problems, 430-431
 preparation of, 421-423
 reactions by, 436-441
 typical, 423-430
Organometalloids, 420-435
Organophosphorus compounds, 428-430
Organosilicon compounds, 841-846
L-Ornithine, 732
Ortho carbon atoms, 272
Orthoformate ester synthesis, 310
Ortho-para directing systems, 359-360
Osazones, 416
Osmotic pressure, 6, 8-9
Ovalbumin, 737
Oxalylacetic acid, 724
Oxalysuccinic acid, 724
Oxazines, 656
Oxazole, 787
1,3-Oxazole, 787
Oxidation, 155-157, 550-571
 by air, 550-557
 of alcohols, 556
 primary, 560-561
 secondary, 560-561
 of aldehydes, 556, 561-562
 of aliphatic side chains, 559-560
 of alkenes, 557-559
 of aromatic nuclei, 555
 to quinones, 564-565
 of aromatic side chains, 555-556
 of hydrocarbons
 saturated, 556
 unsaturated, 552-554
 mechanisms of, 563-564
 by oxygen, 550-557
 by reagents in a solution, 557-566
 of sulfur compounds, 565-566
 of vicinal glycols, 562-564
Oxidation-reduction, 48-49, 488-494
Oxidizing agents, 52-53
1,2H-Oxin, 788
1,4H-Oxin, 788
Oxirane, 787
Oxo functions, 79-85
Oxo process, the, 578, 844

- Oxolane, 787
 Oxonium ions, 45, 125
 Oxy functions, 79-85
 Oxygen
 analogs, 85
 atom, 152, 169
 carbonyl, 414-418
 migrations, 519-521, 528-529
 molecules of, 540
 oxidation by, 550-557
 Oxytocin, 744, 821
 Oxyzenin, 737
 Ozalid process, the, 499
 Ozonides, 168, 553
 Ozonolysis, 552, 771

 PETN, 489, 551
 Palladium chloride, 324
 α -Palmityl- α' - β -distearin, 758
 Pamaquin, 797
 Paneth, Fritz, 533-534
 Pantothenic acid, 830
 Papaverine, 797
Para carbon atoms, 272
 Paraffin, 60
 thermal reactions of, 539-540
 Paraldehyde, 403
 Parathion, 826
 Pasteur, Louis, 613
 Pauli exclusion principle, 21, 26
 Pectins, 721
 Penicillin G, 791, 831
 Pentachlorophenol, 826
 Pentadiene, 67
 Pentaerythritol, 489
 Pentaerythritol monoalkanoate, 766
 Pentaerythritol tetranitrate, 489, 551
 2(R),3(S),4(S),5(S)-2,3,4,5,6-Pentahydroxy-
 hexanal, 625
 Pentamethylene bromide, 434
 Pentamethylglucose, 697, 703
 Pentane, 92, 173
 2,4-Pentanedione, 454
 3-Pentanone, 453
 2-Pentene, 428
 Pentobarbital, 805
 Pentosans, 792
 Pentoses, 707, 792
 Peptides, 736
 Peptones, 738
 Peracetic acid, 592
 Perbenzoic acid, 556
 Perhydrocyclopentanophenanthrene, 778
 Perkin, Sir William, 458
 Perkin condensations, 458-459
 Peroxidation, 568-569

 Peroxides, 53
 Pesticides, 825-827
 Petroleum, 834-840
 cracking, 835-837
 products, 839-840
 refining, 834-839
 reforming, 837-838
 pH indicators, 660-663
 Phenanthrene, 145
 Phenazines, 656
 Phenobarbital, 805
 Phenol, 80-81, 150-152, 171, 283
 acidity in, 148-153
 O-substituted, 526-528
 reactivity toward nitration, 354
 Phenol-formaldehyde polymers, 866-867
 Phenoxide ion, 151, 211
 Phenyl allyl ether, 275
 Phenyl azide, 806
 Phenyl isocyanate, 411
 Phenyl isothiocyanate, 411
 Phenylacetic acid, 213
 L-Phenylalanine, 732
 1-Phenylazo-2-naphthol, 527
 γ -Phenylbutyric acid, 582
N-Phenylcarbamates, 411
 Phenylchlorosilanes, 842
N-Phenyldiazoline, 476
 Phenylethyl bromide, 293, 332
 Phenylethyl halides, 272-273
 Phenylglyoxalanilide, 518
 Phenylhydrazine, 476, 586
N-Phenylhydroxylamine, 526, 583
 Phenylmercuric acetate, 421
 Phenyllosazone, 697
 β -Phenylpropionic acid, 530
 Phenylpyruvic acid, 578
 Phenylsulfonylquadricycloheptane, 307
N-Phenylsulfamic acid, 526
 Phosgene, 121, 122
 Phosphate, 751
 Phosphatidic acids, 766-767
 Phosphatidyl cholines, 766-767
 Phosphatidyl ethanolamines, 766-767
 Phosphatidyl serines, 766-767
 2-Phosphoenolpyruvic acid, 723
 Phosphorescence, 658-659
 3-Phosphoglyceraldehyde, 723
 3-Phosphoglyceraldehyde, 726
 2-Phosphoglyceric acid, 723, 726
 3-Phosphoglyceric acid, 726
 Phosphoinositides, 766-767
 Phosphoproteins, 738
 Phosphoric acid, 221, 299
 Phosphorus halides, 290
 Phosphorus pentoxide, 299

- Phosphosphingosides, 766-767
 Photoelectric spectropolarimeter, 634
 Photolysis, 254
 Photosensitization, 546
 Photosynthesis, 725
 Phthalein dyes, 655-656
 Phthalic anhydride, 555, 865
 Phthalimide, 87, 278
 Phthalocyanine, 686
 Physical properties, 179-195
 Phytol, 808
 Pi orbitals, 34
 Picric acid, 212
 Picryl chloride, 479
 Pimaric acid, 776
 Pinacol, 512, 582, 860
 rearrangement, 289
 Pinacolone, 512
 Pinene, 773
 β -Pinene, 772
 Pinene hydrochloride, 773
 Pinyll cation, 773
 Piperidine, 802
 Piperine, 802
 Pitzer strain, 69
 Pival, 827
 Pivalaldehyde, 489
 2-Pivalyl-1,3-indanedione, 827
 Planar polycyclic systems, 76
 Plane-polarized light, 609
 rotation of, 613
 Plasmalogens, 766-767
 Plasmochin, 797
 Plasticizers, 864
 Plastics, 861-864
 Polar molecules, 676
 Polar protic solvents, 275
 Polar solvents, 255
 Polarimeters, 611, 623
 Polariscopes, 611, 622
 Polarization, in molecules, 209
 Polarized light, 609-611
 Polyacrylonitrile, 863
 Polyalkylation, 278, 280
 Polyamides, 866
 Polyatomic molecules, 31
 Polycaprolactam, 866
 Polycyclic compounds, 593-595
 Polycyclic heterocycles, 802-804
 Polyesters, 865-866
 Polyethylene, 861-862
 Polyethylene oxides, 864
 Polyethylene phthalate, 865
 Polyethylene terephthalate, 865
 Polyformaldehyde, 864
 Polyhalides, 78
 Polyhalomethanes, 335
 Polyisobutylene, 860, 861, 862
 Polymerization, 402-403, 541-542, 838,
 850-864
 coordination, 853-854
 Polymers, 853
 amine-formaldehyde, 867-868
 atactic, 854
 chain length in, 854-856
 condensation, 865-868
 haloethylene, 863
 isotactic, 854
 living, 853
 phenol-formaldehyde, 866-867
 physical modification of, 864-865
 stereoregular, 854
 syndiotactic, 854
 from unsaturated esters, 863
 with hetero atoms in the chain, 863-864
 Polyoxymethylene, 403
 Polyphosphoric acid, 299
 Polypropylene, 862
 Polysaccharides, 715-722
 Polystyrene, 862
 Polysulfide elastomers, 868
 Polyterpenes, 778
 Polytetrafluoroethylene, 848
 Polyurethanes, 411, 868
 Polyvinyl acetate, 863
 Polyvinyl alcohol, 863
 Polyvinyl butyral, 863
 Ponceau red 2 R, 654
 Porphin, 806
 Porphin ring theory, 808-809
 Porphyrins, 806-810
 biological utilization of, 807-808
 occurrence, 807-808
 structures, 808-810
 synthesis of, 809
 system, 806
 Positional isomers, 79
 Positioning systems, 96
 Positive integer, 21
 Potassium, 119
 Potassium benzenecarbohydroxamate, 382
 Potassium bisulfate, 299
 Potassium carbonate solution, 276
 Potassium iodide, 270
 Potassium permanganate, 117
 Potassium phthalimide, 278
 Potassium *tert*-butoxide, 296
 Prefixes, 100-102
 Prehnitenesulfonic acid, 524
 Priestly, Joseph, 725
 Primuline, 657
 Principal energy level, 21

- Progesterone, 782
 Prolamines, 737
 L-Proline, 732
 Propane, 59-60
 Propionaldehyde, 168
 Propiophenone, 529
 Propyl alcohol, 163, 168
 Propyl bromide, 163
 Propyl iodide, 167
 Propylene, 303, 320
 Protamines, 737
 Proteans, 738
 Proteins, 736-748
 chemical properties, 739-740
 classification, 736-738
 coagulated, 738
 conjugated, 736-738
 denatured, 738
 derived, 736-738
 physical properties of, 738-739
 serological assay, 741
 simple, 736-737
 structure of, 741-748
 Proteoses, 738
 Protolytic solvents, 119
 Proton, 122, 205-206
 Proton magnetic resonance (PMR), 187
 Prototropy, 171
 Provitamins, 547, 815
 Pteroylglutamic acid, 816
 Purine, 804, 810-811
 α -Pyran, 788, 796
 δ -Pyran, 788, 796
 Pyranose ring, 704
 Pyrazine, 788
 Pyrethrins, 825
 Pyridazine, 788
 Pyridine, 176, 796
 Pyridoxal phosphate, 751
 Pyriliun salts, 800
 Pyrimidine, 804, 810-811
 Pyrimido-(4,5-b)-quinoxaline-2,4-diol(Benzo-
 [g]pteridine-2,4(1H,3H)-dione), 790
 Pyrocatechols, 157
 Pyrolytic *cis*-eliminations, 304-305
 α -Pyrone, 799
 δ -Pyrone, 799
 Pyronine G, 801
 Pyrophosphate, 826
 Pyroxylin, 716
 Pyrrole, 791, 795, 809
 Pyrrolidine, 787, 796
 1-Pyrroline, 796
 3-Pyrroline, 796
 Pyruvic acid, 723, 724
 Quantum mechanics, 20
 Quantum numbers, 21-22
 Quantum yield, 330
 Quartz prisms, 613
 Quaternary ammonium halide, 301-302
 Quaternary ammonium hydroxide, 301-302
 Quaternary ammonium salts, 86
 Quaternary nitrogen, 301
 Quinacrine, 797
 Quinazoline, 790
 Quinine, 797
 Quinoline, 790, 796, 799
 Quinone dyes, 657
 Quinones, 157
 oxidation of aromatic nuclei to, 564-565
 Quinoxaline, 789
 Quinuclidine, 803
 Racemic hexachlorocyclohexane, 621
 Racemic modifications, 620, 621
 Racemization, 266, 628-629
 in nitrogen compounds, 629
 Radicals
 anions, 545
 benzyl free, 535
 ions, 545
 neophyl, 544
 triphenylmethyl, 536
 See also Free Radicals
 Radii, atomic nonbonding, 37
 Raffinose, 715
 Raney nickel, 574-575
 Raoult's law, 6
 Reaction coordinate, 234-235
 Reactions, *See also* Appendix II
 abnormal bimolecular displacement, 275
 acetylene, 397-398
 of acid chlorides, 379-380
 acid-catalyzed, 254
 of active hydrogen compounds, 448-472
 addition, typical, 321, 325
 of aldehydes, 392-419
 alkylation, 344-345, 504-505
 of anhydrides, 379-380
 autoxidation, 540-541
 azo coupling, 347-348
 base-promoted, 254
 biuret, 740
 the Cannizzaro, 488-489
 chain, 330, 539
 chemical equilibria, 229-243
 Claisen-Schmidt, 458
 collision theory of, 231-232
 consecutive, 240-243
 coupling, 433-434

- Criegee, 562-563
 the crossed-Cannizzaro, 489
 of the cumulated system, 408-409
 Curtius, 312
 cyclization, 385-387, 790
 decarboxylation, 467-470
 of diazo compounds, 501-505
 of diazonium salts, 496-501
 Diels-Alder, 589-594
 electron transfer, 229
 electrophilic aromatic substitution, 362-367
 elimination, 292-312
 alpha, 308-312
 base-promoted, 297-298
 beta, 292-303
 conjugate, 305
 internal replacements, 306-307
 prolytic, 304-305
 endergonic, 237
 epoxidation, 552
 exergonic, 237
 first-order, 231
 free radical, 532-549
 Friedel-Crafts, 344-347, 528, 529
 fundamental types, 226-229
 coordination, 229
 heterolysis, 229
 Grignard, 422
 haloform, 452-454
 halogenation, 362-363
 Hell-Volhard-Zelinsky, 450-451
 homolysis, 537
 insertion, 503-504
 intramolecular, 248-251
 of ketones, 392-419
 Malaprade, 562
 mechanisms, 226, 230, 283-284
 Meerwein-Ponndorf-Verley, 490-492
 Michael addition, 476-477
 molecularity, 231
 ninhydrin, 740
 nitration, 363
 of nitriles, 392-419
 nucleophilic displacement, 371-373
 at unsaturated carbon, 473-487
 Oppenauer, 490-492
 order, 230-231
 organometallic, 431-434, 436-441
 radical, 331-332
 reactivity and rates of, 230-232
 Reformatsky, 438
 Reimer-Tiemann, 367
 reversibility of, 393-394, 460
 Sandmeyer, 499
 Schmidt, 312
 second-order, 231
 side, 286-290, 325-326
 single-step, 233
 stereospecific, 247-248
 stoichiometric, 333
 sulfonation, 363-364
 thermal, 539-540
 third-order, 231
 Tischenko, 490
 transition state theory of, 232-235
 typical, 286
 Willgerodt, 529-530
 Wurtz, 434
 Wurtz-Fittig, 434
 Reactive intermediates, 240
 types of, 243
 Reagents, 284-286
 acid derivatives and, 439-440
 Benedict's, 698
 electrophilic, 130, 147, 338, 340-348
 for eliminations, 296-299
 Grignard, 422-423
 aldehydes and, 437-438
 aryl, 431
 carbonation of, 441
 ketones and, 437-438
 syntheses by addition, 436-437
 for halogenation, 340-342
 Millon's, 740
 for nitration, 342-343
 oxidation by, 557-566
 Tollens', 561
 Red
 cherry, 663
 Congo, 654
 emission and absorption relationships, 650
 Ponceau 2 R, 654
 Redox, 47, 48
 balancing equations, 48-52
 half-cell method, 48
 oxidation number method, 48
 Reducing agents, 53
 Reduction, 155-157, 572-587
 Beauvallet-Blanc, 583
 Birch, 583
 Clemmenson, 582
 of diazonium groups, 586
 of fatty acids, 578-579
 hydrogenation, 572-580
 hydrogenolysis, 572-580
 by metals, 580-584
 miscellaneous agents, 585-587
 of nitro compounds, 585-586
 Rosenmund, 577
 Stephen, 585

- Refluxing temperature, 253
 Reformatsky reaction, 438
 Refractions
 atomic, 607
 group, 607
 of homologs, 607
 index of, 603-608
 measuring, 604-605
 use of, 605-608
 specific, 606
 theory of, 603-604
 Refractometer, 179
 Abbe, 604-605
 immersion, 604
 Reimer-Tiemann reaction, 367
 Resins, 846-847, 861, 866-867
 Resonance, 140-155
 in conjugated systems, 251-253
 electron paramagnetic, 674-675
 energy
 of arenes, 147
 diagram for benzene, 143
 hybrids, 144
 magnetic, 667-675
 detecting, 668-669
 measuring, 668-669
 no-bond, 269
 stabilization, 148-149
 steric inhibition of, 353
 theory of, 144
 Resonance energy, 31, 142-143
 Retinene, 776
 Rhodoxanthin, 777
 Riboflavin, 749-750
 Ribonucleic acid, 812
 Ribose, 709-710
 Ribose-5 phosphate, 726
 Ribulose-1,5 diphosphate, 726
 Ring Compounds, 68-77
 Ring Index, 102
 Ring systems
 five-membered, 791-796
 four-membered, 791
 six-membered, 796-802
 three-membered, 790-791
 Rodenticides, 827
 Rosaniline, 655
 Rosenmund reduction, 577
 Rotenone, 825
 Rubbers
 buna, 860
 butyl, 861
 methyl, 860
 natural, 858-861
 silicone, 846-847
 synthetic, 859-861
 thiokol, 868
 Ruff degradation, 699

 Saccharic acid, 698
 Safronines, 656
 Salicin, 711
 Salicylate ion, 216
 Salmin, 737
 Salts, 46
 arenediazonium, 495
 chromonium, 800
 diazonium, 496-501
 reduction of, 586
 pyrilium, 800
 triphenylpyrilium, 801
 Sandmeyer reactions, 499
 Sandwich compounds, 424-427
 Sanger, Frederick, 741
 Saponification, 135, 378-379, 754
 Saponification number, 754-755
 Saturated compounds, 65
 Saturated hydrocarbons, 556
 Saytzeff rule, 295, 299, 303
 Schiff bases, 418
 Schmidt reaction, 312
 Schmidt rearrangement, 514-515
 Schotten-Baumann procedure, 134, 381
 Scombrine, 737
 Sebacic acid, 381
 Sedoheptulose-7 phosphate, 726
 Selenium dioxide, 585
 Selinene, 774
 Semi-ionic bond, 47
 L-Serine, 732
 Serological assay, 741
 Serum albumin, 737
 Serum globulin, 737
 Sesquiterpenes, 774-776
 Sigma complex, 339, 478
 valence-bond structures of, 478
 Sigma molecular orbital, 33, 140
 Silanes (silicanes), 841-846
 Silicon organic compounds, 841-848
 carbon-functional, 843-844
 uses of, 847-848
 Silicon tetrachloride, 842
 Silicones, 846-847
 oils, 846
 resins, 846-847
 rubbers, 846-847
 waxes, 846
 Siloxane, 846
 Silver cyanide, 267
 Silver ion, 266-267, 270

- Silver nitrate, 267
- Silver oxide, 302
- Simple proteins, 736-737
- Single bonds, 117-127
- Singlet states, 658
- Skeletal isomers, 60
- Skew conformations, 64-65
- Skraup syntheses, 798
- Soap, 754, 761-766
 - invert, 765
- Sodiomalonate ester, 464
- Sodium, 46
- Sodium alkyl sulfate, 764
- Sodium azide, 312
- Sodium bisulfite, 401-402
- Sodium borohydride, 443
- Sodium bromide, 285
- Sodium carboxymethyl cellulose, 717-718
- Sodium cyanide, 267
- Sodium dodecylbenzenesulfonate, 763
- Sodium ethoxide, 296
- Sodium ethyl azaleate, 543
- Sodium hydroxide, 13, 119, 123, 151-152, 257
- Sodium hypohalite, 311
- Sodium iodide, 270
- Sodium laurate, 543
- Sodium nitrate, 267
- Sodium pentothal, 805
- Sodium phenoxide, 275
- Sodium propoxide, 167
- Solvent-separated ion pair, 266
- Solvolysis, 371-391
 - abnormal mechanisms, 383-385
 - of acids, 376-387
 - of acid derivatives, 376-389
- Specific refraction, 606
- Spectra, 184, 186, 639-666
 - absorption maxima, 643
 - absorption minima, 643
 - absorption of light and, 639
 - absorption peaks, 643
 - band, 185
 - in determining structure, 641-645
 - electromagnetic absorption, 185-189
 - electron paramagnetic resonance, 674-675
 - infrared, 186-187
 - absorption of various organic compounds, 188
 - in compounds, 646-647
 - mass, 689-692
 - molecular, 639-652
 - molecular mass, 690-691
 - nuclear magnetic resonance (NMR), 187, 669-674
 - correlation chart for, 192
 - ultraviolet, 641-644
 - absorption of acetone, 186
 - visible, 641-644
- Spectrometers, 692
- Spectroscopic data, 10
- Spectroscopic studies, 21, 241
- Sphingosine, 767
- Spin quantum number, 21
- Spin splitting, 187
- Spiro atom, 76
- Spirostanane, 75-76
- Squalene, 777, 778, 779
- Stable intermediate, 240
- Starch, 719-720
 - digestion of, 722-724
- Statistical mechanics, 20
- Stearic acid, 756
- Stephen reduction, 585
- Stereochemistry, 303
 - of cyclohexanones, 634-636
 - electron-deficient rearrangements, 517-519
 - in free radical reactions, 542
- Stereoisomeric, 336
- Stereoregular polymers, 854
- Stereospecific reactions, 247-248
- Steric factors, 246-251, 359, 360
 - acceleration, 246-247
 - configuration, 248-251
 - conformational effects, 247-248
 - hindrance, 246
- Steric inhibition of resonance, 353
- Steroids, 778-782
 - classification of, 779-780
 - important, 781-782
 - structure of, 779-780
- Stevens rearrangement, 523
- cis*-Stilbene, 644
- Stoichiometric reaction, 333
- Stoichiometry, 254
- Strecker synthesis, 397
- Streptomycin, 831
- Structural formulas, 15
- Structure
 - by analogy, 166
 - determination of, 163-176
 - of ethers and esters, 166-168
 - mesomeric, 172
 - olefin, 168
 - and physical properties, 179-195
- Strychnine, 803
- Sturine, 737
- Styrene, 293, 334-335
- Substantive dyeing, 659
- Substitution, 120
 - electrophilic aromatic, 338-370

- Substrate, 748
 Succinic acid, 724
 Succinimide, 87
 Sucrose
 inversion of, 714
 structure of, 713-714
 Suffixes, 100-102
 Sulfanilic acid, 526
 Sulfates, 275-278
 replacements of, 260-280
 side reactions of, 279-280
 Sulfenyl chloride, 566
 Sulfinic acid, 566
 Sulfonates, 275-278
 esters of, 385
 replacements of, 260-280
 Sulfonating agents, 343-344
 Sulfonation, 154
 reactions, 363-364
 Sulfonic acid, 85, 170, 217-218, 299
 Sulfonic acid derivatives, 288-289
 Sulfonium compounds, 261
 Sulfur analogs, 85
 Sulfur atoms, 170
 Sulfur compounds, oxidation of, 565-566
 Sulfur dyes, 657
 Sulfuric acid, 83, 84, 117, 122, 221, 257, 285
 Sulfurous acid, 157
 Syndiotactic polymers, 854
 Synthesis, principles of, 255-257
 Systems
 aromatic, 76
 conjugated, 67
 cumulated, 67, 407-414
 involving hydride exchange, 488-494
 ortho-para directing, 359-360
 planar polycyclic, 76
 positioning, 96
 unsaturated
 nucleophilic additions in, 436-447
 nucleophilic displacement in, 436-447

 TEPP, 826
 TNT, 551
 TPN⁺, Coenzyme-11, 749
 D-Talose, 707
 Tanner, Howard A., 725
 Tannic acid, 711
 2(R),3(R)-Tartaric acid, 625
 Taurine, 733
 Taurocholic acid, 781
 Tautomeric acetamide, 186
 Tautomerism, 170-172
 Terpenes, 770-778
 structure of, 770
 α -Terpinene, 772

 Terramycin, 831
 Tertiary alcohols, 388
 Tertiary amines, 126, 179
 Testosterone, 781
 Tetraalkylammonium hydroxide, 126
 2,3,4,5-Tetrabromopyrrole, 795
 Tetrachloroethylene, 333
 Tetraethyl pyrophosphate, 826
 Tetraethyllead, 423-424
 Tetraethylsilane, 842
 Tetrafluoroethylene, 848
 1,1,2,2-Tetrafluoro-3,3,4,4-tetrachlorocyclo-
 butane, 596
 Tetrahedral carbon, 247
 Tetrahedral geometry, 79
 Tetrahedron, 32, 262
 Tetrahydric alcohol, 489
 Tetrahydrobenzaldehyde, 593
 Tetrahydrofuran, 787, 796
 Tetrahydrothiophene, 566, 796
 Tetramethylammonium hydroxide, 302
 Tetramethylene sulfone, 566
 Tetramethylene sulfoxide, 566
 Tetramethylglucose, 697, 703
 2,3,4,6-Tetramethylglucose, 713
 Tetramethyllead, 423-424
 Tetramethylsilane, 187, 842
 Tetraterpenes, 776-777
 1,3,9,10-Tetrazanthracene-2,4-diol, 790
 Tetroses, 707
 Thermal agitation, 182
 Thermal cracking, 835
 Thermal reactions, 539-540
 Thermodynamics, 236
 Thermometer, differential, 8-9
 Thermoplastic resins, 861
 Thermosetting resins, 861
 1-Thiaindene, 789
 Thiamin, 816, 830
 Thianaphthene, 789, 791
 Thio analogs, 85
 Thioacetic acid, 335
 Thioaldehydes, 278
 Thioamides, 441
 Thioethers, 261, 335
 Thioketones, 278
 Thiokol rubber, 868
 Thiol esters, 280
 Thiole, 787
 Thione esters, 280
 Thionyl chloride, 84, 166
 Thiophene, 785, 787, 791, 795
 Thiuram disulfides, 826
 Thiuram monosulfides, 827
 Threo configurations, 617
 L-Threonine, 732

- D-Threose, 707
 Thymine, 811, 813
 Thymus histone, 737
 Thyroglobulin, 737
 Thyroxine, 732
 L-Thyroxine, 821
 Tischenko reaction, 490
 Tiselius cell, 739
 α -Tocopherol, 819
 β -Tocopherol, 819
 γ -Tocopherol, 819
 δ -Tocopherol, 819
 Tollens' reagent, 561
 Tollens' test, 156
 Toluene, 276, 836
 energy diagram for, 361
 reactivity toward nitration, 354
 Toluenesulfonic acid, 285
trans-Coplanar, 303
 Transesterification, 373-375
 abnormal, 383-385
 acid-catalyzed, 374
 base-promoted, 373
 energy diagram for, 373-374
trans-Isomers, 66
 Transition state theory, 232-235
 quantitative treatment of, 238-240
 Transoid conformations, 64-65, 68
 Traumatic acid, 822
 Trialkylcarbonium ions, 285
 2,2,2-Tribromoethanol, 492
 2,3,5-Tribromofuran, 795
 Trichloroacetic acid, 209, 310
 Tricyclene, 514
 Trienes, 320
 Triethanolamine, 791
 Triethanolammonium, 765
 Triethylchlorosilane, 427, 842
 Trigonal bonding, 33
 Trihaloketones, 453
 Trihydroxypivalaldehyde, 489
 Triisobutylboron, 428
 Triketohydrindene hydrate, 740
 Trimethoxyglutaric acid, 704
 Trimethylamine, 207, 302
 Trimethylammonio, 126
 Trimethylchlorosilane, 427, 842
 Trimethylene bromide, 307
 2,3,6-Trimethylglucose, 713
 2,2,4-Trimethylpentane, 836
 2,4,4-Trimethyl-1-pentene, 838
 5,7,8-Trimethyltolcol, 819
 Trinitrobenzene, 88
 1,3,5-Trinitrobenzene, 480
 2,4,6-Trinitrochlorobenzene, 479
 Trinitrotoluene, 88, 551
 Triose, 707
 Trioxane, 403
 Trioxymethylene, 403
 Triphenylamine, 219, 221
 Triphenylcarbonium ion, 272
 Triphenylene, 485
 Triphenylmethane dyes, 655-656
 Triphenylmethyl chloride, 272
 Triphenylmethyl radicals, 536
 Triphenylphosphine, 429
 Triphenylphosphinemethylene ylide, 429
 Triphenylpyrilium salt, 801
 Triphosphopyridine nucleotide, 749
 Triplet states, 658
 Triptycene, 485
 Tristearin, 758
 Triterpenes, 776-777
 Tropone ring, 823
 Trypanosomiasis, 421
 L-Tryptophan, 732
 L-Tyrosine, 732

 Ultraviolet spectra, 641-644
 Unimolecular, 231
 Unsaturated carbon, *see* Carbon, unsaturated
 Unsaturated compounds, 65
 hydrogenation of, 576-577
 Unsaturated esters, 863
 Unsaturated hydrocarbons
 hydrogenation of, 574-576
 oxidation of, 552-554
 Uracil, 811
 Urea, 3, 91
 Urete, 787
 Urethanes, 411
 Uric acid, 811

 Valence bond structures, 144-145
 Valence electrons, 26
 Valence rules, 15, 165
 L-Valine, 732
 Van Slyke amino nitrogen determination, 735
 van't Hoff, Jacobus, 79
 van't Hoff factor, 221, 222
 Vapor phase chromatography, 12
 Vaporization, 179
 Vasopressin, 744, 821
 Vat dyes, 657
 Vectors
 forces, 192
 molecular moments and, 676-679
 Veronal, 805
 Vetivazulene, 775
 Vibrational transition, 642
 Vicinal atoms, 292, 320
 Vicinal chlorohydrins, 325

- Vicinal dibromides, 292
- Vicinal dichlorides, 270
- Vicinal dihalides, 277, 292
- Vicinal glycols, 289, 562-564
- Vigneaud, Vincent du, 744
- Vinyl alcohol, 172
- Vinyl bromides, 139-140
- Vinyl halides, 129, 271
- Vinylacetylene, 323
- Vinylation, 326-327, 477-478
- Vinyltrichlorosilane, 843
- Violet
 - crystal, 653
 - emission and absorption relationships, 650
 - methyl, 662
- Viscose, 717
- Visible spectra, 641-644
- Vital force theory, 3
- Vitamins, 815-820
 - A, 776, 830
 - B, 749-751, 816-818, 830
 - C, 710, 819
 - D, 547, 781
 - E, 819
 - functions of, 816-820
 - K, 819-820
 - P, 818
- Vitellin, 738
- Volatile organic compounds, 121
- von Liebig, Justus, 11, 226
- Vulcanization, 859
- Wagner-Meerwein rearrangement, 289, 511-512, 773
- Walden, Paul, 630
- Walden inversion, 262-263, 629-631
- Warfarin, 827
- Water
 - equilibrium diagram of, 8
 - solubility in, 183-184
- Wave mechanics, 20
- Waves
 - electromagnetic, range of, 640
 - of light
 - as perpendicular vibrations, 610
 - vibrations of, 609
- Wavelength
 - color and, 650
 - of light absorbed, 649
- Waxes, 760
 - silicone, 846
- Willgerodt reaction, 529-530
- Williamson synthesis, 277, 845
- Witt theory, 650
- Wittig synthesis, 428-429
- Wohl degradation, 699
- Wöhler, Friedrich, 3
- Wolff rearrangement, 504, 514
- Wolff-Kischner reduction, 506-507
- Wood, constituents of, 725-727
- Woodward, R. B., 747
- Wurtz reaction, 127, 434
- Wurtz-Fittig reaction, 434
- Wurtz-Fittig synthesis, 844
- Xanthates, 304
- Xanthene, 789, 801
- Xanthene dye, 801
- Xanthine, 811
- Xanthophylls, 777
- Xanthoproteic test, 740
- Xanthydrol, 582
- X-ray diffraction, 10, 687-688
- m*-Xylene, 836
- o*-Xylene, 836
- p*-Xylene, 836
- Xylose, 710
- Xylulose-5 phosphate, 726
- Yellow
 - acridine, 656
 - Alizarin R, 654
 - amido E, 656
 - emission and absorption relationships, 650
 - golden, 663
 - Helindon CG, 657
- Ylide, an, 428
- Zahn, H., 744
- Zeaxanthin, 777
- Zein, 737
- Zeisel method, 285
- Ziegler, Karl, 854
- Zinc, 149, 169
- Zinc chloride, 284
- Zingiberene, 774

